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CLINICO - IMMUNOLOGICAL PROFILE OF NEPHROTIC SYNDROME IN CHILDHOOD IN BUNDELKHAND REGION

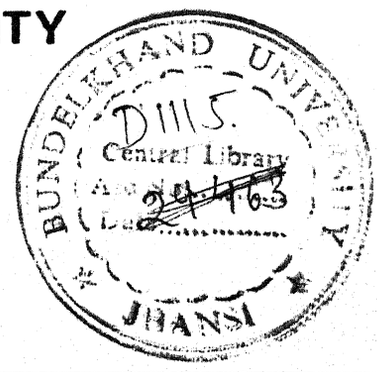
THESIS

For

DOCTOR OF MEDICINE

(PAEDIATRICS)

BUNDELKHAND UNIVERSITY
JHANSI (U. P.)



1994 **SHALABH KUMAR**

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And bringing him to his own,

Is a derned sight better business

Than loafing around the throne".

John Hay -

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C E R T I F I C A T E

This is to certify that the work entitled "CLINICO-IMMUNOLOGICAL PROFILE OF NEPHROTIC SYNDROME IN CHILDHOOD IN BUNDELKHAND REGION", which is being submitted as thesis for M.D.(Pediatrics) Examination, 1994 of Bundelkhand University, by SHALABH KUMAR, has been carried out in department of Pediatrics, M.L.B. Medical College, Jhansi.

He has put in the necessary stay in the department according to university regulations.

Dated: 23.9.93

23.9.93

(Ramesh Kumar)
M.D., D.C.H.,
Professor and Head,
Department of Pediatrics,
M.L.B. Medical College,
JHANSI.

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Dated : 23.9.93

Kaushik

(Anil Kaushik)
M.D.,
Assistant Professor,
Department of Pediatrics,
M.L.B. Medical College,
JHANSI(UP)

(GUIDE)

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Dated: 23·9·93

(Ratna Saxena)
M.D.,
Assistant Professor,
Department of Pathology,
M.L.B. Medical College,
JHANSI(UP),

(CO-GUIDE)

A C K N O W L E D G E M E N T S

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Dated:

Shalabh Kumar

(Shalabh Kumar)

C O N T E N T S

INTRODUCTION

INTRODUCTION

Nephrotic syndrome is the most frequently encountered disease among all nephrologic entities in pediatric age group with incidence reported to be 4-15/ lac. under 16 years of age.

It is the mere clinical manifestation of large number of morphologically distinct glomerular disorders, which in approximately 95% of children result from primary glomerular disease and in 5% due to secondary systemic diseases. Among the primary glomerular, MCNS is the commonest underlying pathology estimated around 52-78% followed by focal glomerulosclerosis and mesengial proliferative around 9-15% (Habib et al, 1971). Children with these glomerular lesions are clinically indistinguishable at presentation with MCNS but show a relative lack of response to the usual regimen of steroid therapy. Except for membranous nephropathy, less common causes like membranoproliferative glomerulonephritis and post streptococcal glomerulonephritis are rarely confused with MCNS. As cause is not identifiable this group, combindely is also known as idiopathic nephrotic syndrome which is predominantly a disease of young children. Sixty percent of the children being between 2-6 years of age suffer from idiopathic nephrotic syndrome. Absence of azotemia, hypocomplementemia, hypertension, hematuria and age 1 to 6-7 years favours the diagnosis of MCNS.

Though most of the patients of MCNS can be separated with characteristic clinical presentation and dramatic response to corticosteroid therapy exact identification of underlying pathology is possible only by microscopic studies. Clinico-pathologic correlation is significant for evaluation of prognostic value of specific pathologic and clinical features as well as management of patients. Association of mesengial hypercellularity and focal segmental sclerosis with clinical presentation of hematuria and hypertension and poor therapeutic response to steroids have been observed by various workers (Habib et al, 1971; White, 1971, ISKDC, 1981 and Saxena et al, 1988).

Various regimens of steroid therapy have been worked out but alternate day regime is said to be associated with least toxicity and relapses.

These patients showed a variable clinical course. Ninety five percent of them respond favourably to corticosteroid therapy and 90-95% of those who respond, have MCNS by renal biopsy but majority of them (— 85%) relapse within one year. Still many (— 25%) relapse frequently ($\bar{7}$2/6 months or $\bar{7}$3/year) and some become dependent to it. A small group do not respond to corticosteroids either initially (initial non responders = 5%) or during a relapse (late non responder 5 = 10%) and have to be treated with cytotoxic drugs. Like cyclophosphamide, cyclosporin A, and chlorambucil. Immunoregulatory drugs like levamisol are also under trial.

Response to steroids is slow in presence of infection, which should include tuberculosis as well as most widely prevalent infection in India and many patients of nephrotic syndrome showing delayed response should be investigated for tuberculosis in addition to other infections.

Minimal change nephrotic syndrome as an immunologically induced disease was first seriously considered in 1907 by Bell and Clawson. Pointers towards immunologic basis are clinical association with respiratory infections and prophylactic immunizations, other atopic disorders (eczema, rhinitis) increased incidence of MCNS in patients with hodgkin's disease (in whom defects in T cell mediated immunity are well recognized), response to corticosteroid and immunosuppressive therapy and spontaneous remission following measles infection or immunization.

Giangiacoma (1975) observed decreased levels of IgG in patients with idiopathic nephrotic syndrome irrespective of the course of disease. This depression in IgG cannot be explained on urinary losses alone. Increased catabolism may play a part. It has been postulated that T cell mediated conversion from IgM to IgG may be defective. Distributed T helper cell fail to direct the B cells, these in turn would continue to produce IgM and no synthesis of IgG would occur. Increased suppressor cells may have a similar role.

It has not been established whether the depression in cell mediated immunity is a primary event or secondary to hypoalbuminuria, hyperlipidemia or zinc deficiency that coexists in these patients, as all these factors are known to depress cell mediated immunity. Abnormal immunogenic response to some unknown stimuli may be a primary event in patients with nephrotic syndrome leading to suppression of T cell function.

The most difficult problem in the care of children with MCNS continues to be the occurrence of frequent relapses in patients who respond initially to steroids. Repeated or continuous administration of steroids although effective is not always free from severe toxicity. MCNS in India differs from west one, in that majority are frequent relapsers and second, that regular presence of alternate day steroid therapy in inducing longer remission may not be impressive.

Clinically, presence of hematuria, azotemia or hypertension is not helpful or their identification but increased incidence of atopic disorders (asthma, eczema) or rhinitis, less relapses in first few months of induction of first remission, biochemically impaired concentration capacity of urine (as evident by low urinary osmolality) and immunologically persistently low IgG levels and raised IgM levels are among the features linked with early identification of frequent relapsers.

Although etiology of MCNS is still obscure, the

association of nephrotic syndrome with certain morphological immunological and biochemical abnormalities have lead to a better understanding of this disease in recent times. Attempts to correlate the course of the disease with the histologic findings have met with only limited success. The presence of either mild mesangial proliferation or focal tubular changes on renal biopsy is associated with a decreased rate of initial response to intensive prednisolone treatment. At present therefore potential frequent relapsers cannot be identified from histopathologic characteristics.

Preventing the occurrence of frequent relapsers and until that is possible, finding more effective and safer methods of treating them thus remains the major unsolved problem in case of patients with minimal change nephrotic syndrome (MCNS).

It is in the light of these observations, that the present venture has been undertaken to study incidence, mode of onset, clinical presentation, biochemical, histopathological and immunological changes and to search for clinical or immunological basis to identify frequent relapsers early, which shall permit investigations that might explain the striking mysterious variations in course of patients with MCNS, who at the onset of their disease appear to share similar characteristics. Future needs are the identification of markers for predicting methods for preventing and safe effective drugs for treating the frequent relapses of MCNS.

AIMS OF THE STUDY

1. To study the incidence of nephrotic syndrome in paediatric age group, its clinical presentation and symptomatology.

2. Evaluation of biochemical and metabolic changes that take place in nephrotic syndrome.

3. To study clinico-pathologic relationship in patients having poor steroid response or atypical clinical presentation.

4. Evaluation of response to alternate-day steroid regime and cytotoxic drug therapy and identification of steroid resistant and dependent patients.

5. Analysis of changes in serum IgG, IgM, C_3 and C_4 levels in nephrotic syndrome.

6. Recognition of frequent relapsers and search for clues for their early identification.

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

Munk (1913) coined the term 'Lipoid nephrosis' to describe the condition in patients who had nephrotic syndrome clinically, but whose disease he considered to be a degenerative process of tubules, not involving glomeruli. The term now refers to uncomplicated primary nephrotic syndrome with no glomerular change by light microscopy. In association between mesengial proliferation and nephrotic syndrome was first suggested by Drummond et al (1966), but was not recognized until reported by Churg et al (1970). Importance of focal glomerulosclerosis in relation to corticosteroid resistance and progression to end stage renal disease was described by Churg et al (1970), in a report for International Society for Kidney diseases in children, 1970.

EXTENT OF THE PROBLEM

Nephrotic syndrome is the most frequently encountered disease among all nephrologic entities.

Nephrotic syndrome develops in approximately 1 in 50,000 children under 16 years as reported by Schlesinger and Rothernberg (1968).

Verneir (1987) reported incidence of Idiopathic nephrotic syndrome with an increased preponderance in males. Literature from west as well as India reveals similar figures (Phadke and Bhave et al, 1990).

Cameroon reported that primary disease accounts for over 95% of cases of nephrotic syndrome diagnosed in children over 1 year of age and 80% of cases in adults.

Minimal change nephrotic syndrome is the commonest type encountered in pediatric practice. It's incidence is known to vary in different populations being 2-3/1 lac children aged less than 15 years per year in Europe and north America (Srivastava et al, 1975), but 11/1 lac per year in Arab children in Libya (Lilenfield, 1980).

Study rrom Indian subcontinent confirmed Birmingham's statistics, that as in western countries, more than 70% of children presenting with nephrotic syndrome will eventually prove to be having MCNS. It has also been reported that minimal change disease is a more common cause of nephrotic syndrome in Asians than black children in a South African community.

Habib et al (1973) and ISKDC reported that MCNS is the most common pathological entity underlying nephrotic syndrome in Pediatric population.

Incidence of MCNS among Asians is 9.4/1 lac per year and among non Asians, 1.3/1 lac/year. No subpopulation of Asians defined by language religion, or birth place seemed to be a t special risk of developing nephrotic syndrome (Feehally and Kendall, 1985).

GENETIC PREDISPOSITION

Habib et al (1968) reported familial tendency to acquire nephrotic syndrome in 2-8% of cases.

Affected sibs were found in 3-5% of nephrotic syndrome patients (Moncrieff, 1973).

Habib et al (1973) reported that 3.3% of their patients had affected sibs.

Mc Lean, Makker, Michael et al (1974) reported incidence 1000 times greater, the incidence of nephrotic syndrome in siblings. Histological lesions were also same in them.

Familial occurrence of idiopathic nephrotic syndrome was observed in 3.3% of cases and increased frequency of HLA/B-12 and HLA-A_1/B-8 has been described in several series of patients with MCNS as reported by Robin et al (1981).

Elzonski (1984) reported that 2.7% children in Arabs had affected sibs.

Male : female ratio was described as 2 : 1. Heymann et al (1972) reported this incidence to be almost 1 : 1.

White (1973) also speculated inherited predisposition as a causative factor for the disease. An European survey which excluded cases of congenital nephrotic syndrome found that 63 to 1877 nephrotic children had affected family members.

Clara C Lagneruela (1990) provided additional evidence for an inherited basis for development of steroid sensitive nephrotic syndrome and suggested that this may involve an abnormality of immune system mediated by the major histocompatibility complex.

Whether there is a distinctive polygenic and/or environmental etiology for the development of tendency for familial nephrotic syndrome has not yet been elucidated.

ETIOLOGY

Etiology of commonest variety of nephrotic syndrome MCNS remains an enigma.

Though the definition of nephrotic syndrome remains unchanged - massive proteinuria, hypoalbuminemia and oedema but precise histologic classification of glomerular diseases associated with nephrotic syndrome had drastically improved over the past 10-15 years. The nephrotic syndrome is now a mere clinical manifestation of a large number of morphologically distinct glomerular disorders which in approximately 90% of children, result from primary glomerular disease and in 10% are secondary to systemic disease.

CAUSES OF NEPHROTIC SYNDROME IN CHILDREN

1. Primary renal causes (90-95%) (Idiopathic).
    a. Minimal change nephrotic syndrome (MCNS).
    b. Mesengial proliferative disease.
    c. Focal and segmental glomerulosclerosis (FSGS).
    d. Immune complex glomerulonephritis.
        i. Membranoproliferative glomerulonephritis.
        ii. Acute post streptococcal glomerulonephritis.
        iii. Membranous nephropathy.
    e. Congenital nephropathy.

e. Congenital nephropathy.

2. Systemic Causes (5-10%)

a. Infectious :

Malaria	Syphilis
Hepatitis B	Schistosomiasis
Filariasis	Infectious mononucleosis.
HTLV-III infection	

B. Toxins/Drugs :

Mercurials	Bismuth
Gold	Trimethadione
Probenecid	Renographic medium
Penicillamine	Street heroin
Captopril	Antivenoms

c. Allergies :

Bee sting	Poison oak
Serum sickness	Inhaled pollens
Food allergy	

d. Cardiovascular :

Sickle cell disease

Renal vein thrombosis

Passive congestive heart failure.

e. Malignancies :

Hodgkin's disease	Leukemia
Carcinomas	Wilm's tumor
Melanoma.	

f. Heredofamilial disease :

Diabetes mellitus	Nail patella syndrome
Lipodystrophy	Fabery's disease
Alport's syndrome	Good posture's syndrome

g. Multisystem disorders :

Amyloidosis	Systemic lupus erythematosis
Henoch Schonlein purpura.	
Sjogren's syndrome	Rheumatoid arthritis
Sarcoidosis	Dermatomyositis

IDIOPATHIC NEPHROTIC SYNDROME

Diagnosis of idiopathic nephrotic syndrome (primary) is arrived at by exclusion of known causes of nephrotic syndrome such as infection, drug exposure, malignancy, multisystemic disease. The idiopathic forms are further classified by renal biopsy. Children need not always be subjected to renal biopsy since careful clinical study can often lead to accurate diagnosis.

Approximate incidence of primary disease is 90-95% in children and 60% in adults. While approximate incidence of systemic disease is 5-10% in children while 40% in adults.

MINIMAL CHANGE NEPHROTIC SYNDROME

'Lipoid nephrosis' was the original term coined by Munk which now refers to uncomplicated primary nephrotic syndrome with no glomerular change by light microscopy.

other descriptive titles are nil (nothing to light) disease or microscopy, foot process disease, idiopathic primary nephrotic syndrome. Based unselected renal biopsy studies of children with nephrotic syndrome, MCNS was found to be histologic lesion in 52-78% of cases (White, 1970; Hayslett et al, 1973; and Habib, 1974).

There are no deposits of immunoglobulins or complement in the kidney. Fusion of foot processes seen on electron microscopy was once thought unique to this syndrome but has been reported in many conditions associated with severe proteinuria.

Saxena and Andal et al (1988) reported minimal change lesion in 68.3% of the 66 patients with idiopathic nephrotic syndrome.

Stanely and Robbins, MD, estimated the incidence of MCNS around 65% in children and 15% in adults.

FOCAL GLOMERULOSCLEROSIS

Mesengial Proliferative

These two are additional histoloigic lesions often discussed with MCNS are mesengial proliferation and focal glomerulosclerosis. Children with these lesions are clinically indistinguishable at presentation from those with MCNS except for a lack of response to usual regimen of prednisolone therapy. These patients comprised additional 9-15% of the total children with nephrotic syndrome (Habib, et al, 1974).

Saxena et al (1988) reported the incidence of focal segmental glomerulosclerosis (FSGS) around 10.6% as focal sclerosis patients have biopsy picture similar to MCNS, it is considered by some as its variant. Stanely Robbins (MD) reported incidence of FSGS to be about 10%.

MEMBRANOPROLIFERATIVE AND MEMBRANOUS GLOMERULONEPHRITIS

Saxena et al (1988) reported incidence of membranoproliferative glomerulonephritis in 13.6% and 7.5% of membranous glomerulonephritis in their study.

Idiopathic nephrotic syndrome has also been classified by Rance et al (1976) as :

1. Minimal change nephrotic syndrome.
2. Focal glomerular sclerosis.
3. Diffuse proliferative glomerulonephritis.
   - Type I - Membranoproliferative/mesengio capillary.
   - Type II - Mesential proliferative
   - Mesengial proliferative with crescents.
4. Membranous nephropathy.

PATHOGENESIS

Pathogenesis of MCNS largely remains unclear till now even. Nephrotic syndrome is marked by :

a. Massive proteinuria
b. Hypoalbuminemia
c. Oedema (generalized)
d. Hypercholesterolemia
e. Hypercoagulable state.
f. Increased risk of infections
g. Hypovolumia
h. Elevated BUN and serum creatinine
i. Hypocalcemia.

MASSIVE PROTEINURIA

This is the hall mark ot nephrotic syndrome, starting ot the chain of events leading to picture what is known as nephrotic syndrome.

The syndrome is rundamentally the result of excessive glomerular permeability to plasma proteins and thus heavy proteinuria is its prime characteristics. The biochemical and ultrastructural mechanisms underlying such increased protein leakage vary in the different diseases causing the syndrome.

LOSS OF GLOMERULAR POLYANION

Glomerular basement membrane is principal structure with thick central electron dense layer - Lamina densa and 2 peripheral electron luscent layers - Lamina vara interna and externa which prevents filteration of macromolecules i.e. beyond molecular weight 70,000 and radium 3.6 nm. Filtration of macromolecules across glomerulus disease with increasing effective molecular radius approaching zero at a radius of approximately 3.5 nm. There is thus size dependent permeability barrier in the glomerulus. GBM is the principal structure responsible for this size discrimination (Farguhar et al, 1982).

In addition to size glomerulus can discriminate among molecules according to their charge, allowing greater penetration of neutral and cationic molecules compared with anionic molecules of the same size (Deen et al, 1982 and

Venketachalam et al, 1978). This charge dependent restriction is important in the virtually complete exclusion of albumin from filtrate, since albumin is an anionic molecule of a PI ± 4.5.

GBM is composed of :-

i. Collagen (type IV).

ii. Laminin

iii. Polyanionic proteoglycans particularly heparan sulphate this account for so called glomerular polyanion responsible for charge dependent glomerular filtration barrier (Farguhar et al, 1982).

iv. Entactin

v. Fibronutin

vi. Anionic sialoglycoprotein - coats the surface of endothelial and visceral epithelial cells So charge selective barrier of polyanionic proteoglycans and sialoglycoproteins facilitate filtration of cationic proteins and restricting anionic molecules (albumin). Loss of such anionic sites result in charge selectivity and leakage of anionic molecules such as albumin.

Experimentally, infusion of polycationic molecules such as protamine sulphate which neutralizes anionic sites leads to reversal of albuminuria (Vehaskari et al, 1982).

There is now evidence of loss of charge selectivity in lipoid nephrosis (Dean et al, 1982) what brings about the loss of anionic sites is unknown, but the phenomenon seems also be occur in other glomerular disorders such as diabetic

nephropathy and congenital nephrosis (Cotran et al, 1983 and Michael et al, 1981).

Chang et al (1975) stated that GBM distinguishes molecules on basis of size, Boherer (1978) on basis of shape and Rennke et al (1977) on basis of charge.

Blan et al (1973) also proposed that loss of fixed negative ions situated in the sialoprotein layers of glomerular capillary loop leads to increased permeability of low molecular weight polyanionic proteins as albumin.

Experimentally alteration of the highly negative charged GBM results in fusion of epithelial foot processes and loss of interpeduncular filtration sites (Andrews et al, 1979; and Seiler et al, 1975).

In contrast in acute and chronic glomerulonephritis there is structural damage to the glomerular basement membrane (Hulme et al, 1968; and Tiggler et al, 1979).

In these conditions large molecular weight proteins may cross the glomerular basement membrane at areas of structural damage, resulting in poorly selective proteinuria such as commonly found in patients with acute and chronic nephrosis as well as with focal glomerulosclerosis. These two independent alterations of GBM may explain the difference in response to therapy by some patients.

In some patients the fixed negative charge of the GBM may be restored with therapy, but continued alteration in the glomerular pore size may allow persistence of proteinuria even though hypoalbuminemia and edema have resolved.

T Cell Dysfunction

Recently interest has turned to the possibility that MCNS may be related to T cell dysfunction in which humoral factors perhaps lymphokines are produced which alter GBM permeability(Shaloub et al, 1974; Sasdelli et al, 1980).

This hypothesis is based on observations of spontaneous remissions occurring during the course of measles or following live measles vaccination (Yuceoglu et al, 1969), alteration in immunoglobulin levels with elevation of IgM and depression of IgG (Giangiacomo et al, 1975). Relapse of disease have been reported in association with seasonal allergies and atopic disease (Thomson et al, 1976).

Ariela Benigni et al (1990) made an evaluation of possible relation between renal thromboxane (Tx) A_2 synthesis (measured as urinary secretion of T x B_2). Urinary T x B_2 was significantly higher in MCNS than in healthy controls and reached its maximum at the time of peak proteinuria. Even during remission, urinary excretion of T x B_2 was still significantly higher than in healthy controls. Results suggested that renal T x A_2 could be regarded as one of the possible mediators of the altered glomerular permeability to proteins in MCNS.

b. MARKED HYPOALBUMINEMIA

This is one of the major characteristics of nephrotic syndrome with the serum albumin usually measuring 2.5 g% or less. Massive urinary loss of albumin is

undoubtedly or major factor in the hypoalbuminemia, but decreased synthesis, increased catabolism or extrarenal losses are additional factors which have been incompletely studied to date. Whatever its cause, heavy proteinuria leads to depletion of serum albumin levels below the compensatory synthetic abilities of liver, with consequent hypoalbuminemia and a reversed albumin globulin ratio.

c. EDEMA

The generalized edema is, in turn, the consequence of the loss of colloid osmotic pressure of blood and the accumulation of fluid in the interstitial tissues. There is also sodium and water retention, which aggrevates edema. This appears to be due to :

i. Compensatory secretion of aldesterone, mediated by hypovolumia enhanced antidiuretic hormone secretion.
ii. Stimulation of the synthetic system.
iii. Primary renal effect of uncertain nature.

The decreased calloid osmotic pressure leads to net movement of fluid from vascular system into interstitium or into the 'third space' or from arterial compartment of the vascular space into the chambers of heart or into venous circulation, itself leading to reduction in effective arterial blood volume. This leads to retention of salt and water is insufficient to restore and maintain effective arterial blood volume, it continues, and edema develops.

Edema is characteristically soft and pitting. Most marked in periorbital regions and dependent portions of body. It may be quite massive with pleural effusions and ascites or condition termed anasarca.

HYPERLIPIDEMIA

Hyperlipidemia is a striking feature of nephrotic syndrome. It was first described by Epstein (1913) as a feature of nephrotic syndrome. Patients with nephrotic syndrome have multiple abnormalities of lipoprotein metabolism but the cause and exact nature of these abnormalities are uncertain Jorge Joven et al (1990). Genesis of hyperlipidemia in nephrotic syndrome is complex(Bernard,1982).

Lipoproteins are divided in 4 major groups viz.

1. Chylomicrons.
2. Very low density lipoproteins (VLDL) or prebeta lipoproteins.
3. Low density lipoproteins (LDL) or beta lipoproteins.
4. High density lipoproteins (HDL) or alpha lipoproteins.

- LDL are carrier proteins mainly of cholesterol 90% and some amount of triglycerides 10%.
- VLDL are mainly the carrier of triglycerides.

There is a close inverse relationship between hyperlipidemia and serum albumin levels. Low serum albumin levels or diminished plasma oncotic pressure stimulates increased synthesis in liver of cholesterol rich LDL and in more severe cases triglycerides rich VLDL. There is also decreased catabolism of these lipids.

The major carrier of plasma cholesterol LDL and major plasma triglyceride carrier VLDL are elevated early in nephrotic syndrome.

Indirect evidences suggest increased hepatic synthesis of LDL is primary cause of hypercholesterolemia.

VLDL shares same synthetic pathway as albumin in the endoplasmic reticulum and golgi apparatus of the hepatocyte.

Under normal circumstances, VLDL —(Lipoprotein lipase)— LDL

1. Low albumin concentration and accumulation of free fatty acid | Lipoprotein lipase activity.
2. A potent stimulator of lipoprotein lipase activity i.e. plasma apoprotein (apo C-III) is in very low concentration owing to its loss in urine.

Thus hypercholesterolemia and hypertriglyceridemia in nephrotic syndrome results not only from excess production but also from defects in catabolism of phospholipids.

Baxter and Goodman et al (1960) reported that plasma cholesterol becomes elevated as serum albumin concentration drops below 3 g% but triglycerides remain normal until serum albumin is 1 g% or less.

Thus hypercholesterolemia in nephrotic syndrome cannot be explained on one factor, it seems that multiple factors like :

1. Raised LDL.
2. Hypoalbuminemia
3. Decreased lipoprotein lipase activity.
4. Raised alpha and beta globulins in serum are

responsible for its (Bhandari and Mandowara, 1980).

ATHEROSCLEROSIS

Although evidence is strong that increases in total and LDL cholesterol are important in the pathogenesis of atherosclerosis in general population, the extent to which hyperlipidemia contributes to the development and progression of atherosclerosis in patients with nephrotic syndrome is unclear. The duration of exposure to lipid abnormalities induced by the nephrotic syndrome must be taken into account, since atherosclerosis evolves over an extended time. Although incidence of atherosclerotic vascular disease appears to be higher in patients with persistent long standing nephrotic syndrome the presence of hypertension, hypercoagulability and other risk factors for vascular disease makes it difficult to define the role of hyperlipidemia in vascular disease associated with nephrotic syndrome (William et al, 1990).

Dietary measures to reduce serum lipid concentrations are often unsuccessful, whereas newer antilipemic agents may be effective (Vega et al, 1988; and Rabelink et al, 1988).

Simvastatin reduces hyperlipidemia sssociated with nephrotic syndrome (Davison et al, 1984). It is effective and safe in long term management of nephrotic hyperlipidemia and may induce partial remission in nephrosis (Robelink et al, 1990).

'Lipiduria' follows hyperlipidemia, since not only albumin molecules but also lipoproteins leak across the glomerular capillary wall. Lipid appears in the urine either as free fat or as 'oval fat bodies' representing lipoprotein resorbed by tubular epithelial cells and then shed along with degenerated cells.

HYPERCOAGULABLE STATE

Hypercoagulable state is due, in part to loss of anticoagulant factors (antithrombin III) and anti plasmin activity through the leaky glomerular in urine and there are also thrombocytosis and marked increase in serum factors V, VIII and VII and fibrinogen due to increased synthesis or a reduced volume of distribution (Kauffman, 1978; Vaziri, 1984).

Renal vein thrombosis, once thought to be a cause of nephrotic syndrome, is most often a consequence of this hypercoagulable state (Wagoner et al, 1983). In patients with nephrotic syndrome there is increased incidence of renal vein thrombosis (Kendall, 1971; Vaziri, 1983).

More recently, a report of increased platelet aggregation in patients with nephrotic syndrome has again suggested the presence of a hypercoagulable state (Lundin et al, 1980). This report found increased levels of beta thromboglobulin, a platelet specific protein released upon platelet aggregation in patients with nephrotic syndrome.

INCREASED RISK OF INFECTIONS

These patients are particularly vulnerable to infections, especially with staphylococcus and pneumococci. The basis of this vulnerability could be related to loss of immunoglobulins to low molecular weight complement components (Factor B) in urine.

Infections such as septicemia, cellulitis, peritonitis and pneumonitis can occur due to streptococcus pneumonie.

However, an almost equal number of inpatients are caused by gram negative organisms as E.coli, pseudonomas and H. Influenze.

Prophylactic antibiotic therapy is not indicated but close observation for potential infection during the time of edema is essential in children especially who develop fever.

Other reasons proposed for increased susceptibility to infections in patients with nephrotic syndrome are :-

a. Loss of gamm globulins in urine (Barret et al, 1972).
b. Loss of C_3 PA in urine (Michael and McLean et al, 1973).
c. Abnormal macrophage function because of lipid ingestion.
d. Sluggish circulation because of edema.
e. Suppressed immunity due to steroid therapy (Chicken Pox and rubeola intections).

Earlier pneumococcal infections were commoner but now gram negative organisms predominate(Wilfret et al, 1968 and Speak et al, 1974).

With edema insignificant scratch or abrasion of skin can cause cellulitis.

Peritonitis may result when ascites is present compression of lung by pleural effusion and elevation of diaphragm by ascites increase the susceptibility to pneumonia.

HYPOVOLEMIA

Hypovolemia may cause postural hypotension, acute renal failure or circulatory collapse (Reader et al, 1962).

HYPOCALCEMIA

Patients with nephrotic syndrome often have a falsely low levels of serum calcium because of the hypo-albuminemia. But the chronic nephrotic syndrome patients may demonstrate symptoms of hypocalcemia secondary to low ionized serum calcium.

Mechanism of hypocalcemia is still uncertain but blood levels of 25 hydroxy vitamin d, 1, 25 hydroxy vitamin D and 24, 25 dihydroxy vitamin D have all been reported to be significantly low in patients with nephrotic syndrome owing to loss of vitamin products in urine (Paul et al).

More recently diminished intestinal absorption true hypocalcemia, low circulating calcidol levels, secondary hyperparathyroidism have been noted. Most alterations noted are transient and normalised on remission.

Children with relapsing protracted nephrotic syndrome are at risk of developing metabolic bone disease.

Clinically, a few children with MCNS with onset between 1-2 years develop rickets (Bernard, 1982).

PROVOCATIVE FACTORS

Allergic Disorders

Meadow et al (1981) reported positive history of an allergic disorder in 34% children with nephrotic syndrome. Positive history was present in 31% children with relapsing nephrotic syndrome.

Disorders noted were asthma, eczema, recurrent urticaria, hay fever and allergic rhinitis.

In 50% of these children at least one of these allergic disorder was present in first degree relatives of the patient. This was significantly higher incidence of allergic disorder in first degree relatives of control group.

Seasonal factors

Meadow et al (1981) reported that onset of nephrotic syndrome was less common in April, May and June. This was the pollen season in this region, whereas house dust mite another common allergen was commoner in Sept. and October. They could not associated this with timing of occurrence of nephrotic syndrome.

Upper Respiratory Tract Infection

This was a consistent fact given by the parents that onset of nephrotic syndrome or relapse of nephrotic syndrome was preceeded many a times by cold or less often

cough. Relapses occurred usually within 3 days of such upper respiratory tract symptoms.

Fifty percent of relapsing nephrotic syndrome patients had such history two times and 25% of relapsing nephrotic syndrome gave history of upper respiratory tract infection prior to every relapse (Meadow et al, 1981).

HISTOPATHOLOGY

Idiopathic nephrotic syndrome has been classified on histopathological basis as :-

a. Minimal change nephrotic syndrome.
b. Focal or segmental glomerular sclerosis.
c. Diffuse proliferative glomerulonephritis.
   i) Membranoproliferative/or mesengiocapillary type I, type II and type III.
   ii) Mesengial proliferative.
   iii) Mesengial proliferative with crescents.
d. Membranous nephropathy.
e. Congenital nephrotic syndrome.

MINIMAL CHANGE NEPHROTIC SYNDROME(MCNS)

Thus entity accounts for around 65% cases of nephrotic syndrome. Nephrotic syndrome is associated with diffuse loss of foot processes of epithelial cells in glomeruli that appear virtually normal by light microscopy (Phadke et al, 1990). Pre-requiside for the diagnosis of MCNS at light microscopy is exclusion of abnormal findings. Electron microscopy reveals fusion of foot processes.

Etiology of MCNS remains an enigma but several features of disease point to immunological basis.

There is loss of negative charge which is associated with :

1. Enhanced filtration of circulating polyanions, mainly albumin due to loss of heparin sulphate, proteoglycan.
2. Change in shape of epithelial cell leading to familial disappearance of foot processes due to reduction of sialoglycoprotein cell coat.

Saxena (1988) studied 45 patients of MCNS with 42% showing no significant morphological alterations while 44.7% showed mild mesengial alterations in the form of mesengial hypercellularity (1+) and mesengial thickening and in 15.1% focal glomerular obsolescence.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS(FSGS)

It accounts for 10-15% of cases of nephrotic syndrome. Churg et al (1970) first brought this entity to light. It was noted that a small proportion of children responded poorly to steroids and in these renal biopsies showed occasional glomeruli exhibiting an area of sclerosis confined to only one segment of glomerulus.

Habib (1973) divided FSGS in two groups :

a. Focal and segmental sclerosis.
b. Focal glomerular obsolescence.

In focal and segmental sclerosis changes are first apparent in juxta medullary glomeruli and are limited to part of stuff. In focal glomerular obsolescence 15%

glomeruli are completely sclerosed and there is interstitial and tubular damage.

The characteristic degeneration and focal disruption of visceral epithelial cell is thought to represent accentuation of the diffuse epithelial cell change typical of lipoid nephrosis. It is thus pronounced epithelial damage that is the hallmark of FSGS.

Saxena (1988) found on light microscopy FSGS in 10.6% of cases. Studies showed in 4 cases minimal glomerular changes of diffuse mesengial hypercellularity and later focal sclerosing lesion on subsequent biopsy. In two cases glomeruli showed global sclerosis with presence of crescents 28.5% and synechie 20% and intense infiltration of interstitium by mononuclear cells. Small areas of hyalinosis in sclerosed segment were found in almost all cases.

Increasing evidence shows that these represent variations of the disease rather than separate entity. Thus several of these changes may be present in the same biopsy. Alternatively a patient showing MCNS in first biopsy may subsequently show FSGS (Waldnerr, 1983).

Whether FSGS represents a distinct disease or is simply a phase in the evolution of a subset of patients with lipoid nephrosis is a matter of debate with most investigators favouring the latter possibility (Goldzer et al, 1984; Rosen et al, 1981).

Presence of even a single segmentally sclerotic glomerulus in a biopsy specimen warrants for diagnosis of FSGS.

FSGS in contrast to MCNS is often resistant to steroid therapy and carries a substantial risk of progression to end stage renal disease. Repeated renal biopsy may point out the progression of initially MCNS diagnosed patient to FSGS or initially biopsy may have missed glomeruli with already existing sclerotic lesions. Alternatively it is considerable that although FSGS was indeed absent at the time of biopsy abnormal pathogenic process had already come into play in this unique subset of MCNS, leading subsequently to development of morphologically identifiable FSGS detected only on re-biopsy.

DIFFUSE PROLIFERATIVE GLOMERULONEPHRITIS

Membranoproliferative/Mesengio capillary glomerulonephritis (MPGN)

This condition was first described in 1965. By light microscopy, it is seen that GBM is thickened often focally, most evident in peripheral capillary loops, glomerular capillary wall shows double contour or tram track appearance evident on PAS stains.

MPGN has two main types (I and II).

Type I MPGN (Two thirds of cases)

It is characterised by subendothelial electron dense deposits. Most cases of type I MPGN present evidence of immune complexes in glomerulus and activation of both

classical and alternate complement pathway.

Type II MPGN

Dense deposits are present in lamina densa of GBM(intramembranous). Most patients with type II have abnormalities which suggest primary activation of alternate complement pathway (normal C_1 and C_4 and diminished factors and properdin.

Type III MPGN

It is very rare entity. Exhibits both subendothelial and subepithelial deposits, associated with GBM disruption and reduplication.

Mesengial Proliferative Disease

Association between mesengial proliferation and nephrotic syndrome was first suggested by Drummond et al (1983). But it was not well recognised until reported by Churg et al, the ISKDC. There is only slight diffuse increase in mesengial cells together with a moderate increase in mesengial fibrils from 2.5 to 5.3% of patients with nephrotic syndrome will have this lesion on renal biopsy (Habib et al and Anderews et al).

Membranous Glomerulonephritis (MGN)

Light microscopy reveals diffuse deposits giving the appearance of 'Spikes' on the epithelial side of capillary GBM and absence of cellular proliferation. Children may have this disease but it is common in adult

only. It accounts for less than 5% of cases of idiopathic nephrotic syndrome in children.

MGN occurs in 10% of patients with SLE. It is also associated with certain infections (syphilis, malaria, hepatitis B) mercury, gold penicillamine), and tumors(Lung, carcinoma, melanoma)(Arnaut et al, 1982). In 85% of patients with MGN none of these associated conditions exist and term idiopathic MGN is used in such cases (Noel et al, 1979).

It is supposed to be a form of chronic antigen antibody mediated disease. Circulating immune complexes are found in 15-25% of cases (Couser et al, 1982). Only in small number of cases specific antigens have been identified in the deposition.

CONGENITAL NEPHROTIC SYNDROME

It may appear in first 3 months of life. In both the hereditary (Finnish) and sporadic forms the glomeruli may appear to be normal. Dilatation of the proximal convuluted tubules gives a characteristic 'microcystic' appearance and as disease progresses.

Minimal lesion nephrotic syndrome and focal glomerulosclerosis also can begin in first year of life (Kaplan, 1974).

RENAL BIOPSY IN NEPHROTIC SYNDROME

Renal biopsy is usually not indicated in children with steroid sensitive nephrotic syndrome because about 95% have minimal change lesion with an excellent long term

prognosis (Bernstein, 1981).

ISKDC (1982) recommended that occurrence of frequent relapses is not in itself an indication for either an initial or repeat renal biopsy since 95% of 521 children with nephrotic syndrome had 3 or more relapses in first 6 months after initial response.

In frequently relapsing cases responding to steroid therapy, having developed severe steroid toxicity, growth retardation, cataract, severe cushingoid.

Syndrome or failure of steroids to induce remission form sufficient ground to perform renal biopsy. Diagnosis should be revised to focal glomerulosclerosis or mesengial proliferative disease etc and then patients given a trial of cyclophosphamide.

It was a policy of Bruce and Mcdonell et al (1976) to do biopsies in those nephrotic children who were less than 1 or more than 6 years of age or who failed to respond to an initial 2 weeks course of corticosteroids given in a daily divided doses as they found 60% of ultimately steroid responsive patients who showed resolution of proteinuria with 2 weeks of therapy so only a minority of patients had biopsy.

Renal biopsy is necessary before instituting cytotoxic drug therapy in cases suspected other than MCNS since steroid therapy is ineffective and it may even be harmful (Cameron, 1968).

Biopsy should be performed in any patients who has become steroid resistant and in children with frequently

relapsing disease with serious side effects of steroids.

In children aged 9 to 12 months or over 10 years the proportion of cases due to MCNS is smaller but routine biopsy.

Meadow et al (1981) reported that out of 84 steroid responsive children, in 41 renal biopsy showed minimal change. In rest biopsy was not undertaken as they were likely to show histological lesion other than minimal change because their clinical course and findings were even more typical of MCNS than 41 who underwent biopsy.

ISKDC (1981) reported that 25% of all non responders to steroids showed MCNS lesion on biopsy.

In absence of these findings it is reasonable to assume that the disease is minimal lesion and biopsy is not necessary before the start of treatment.

IMMUNOFLUORESCENT STUDIES

Minimal change nephrotic syndrome

Characteristically there are no deposits of immunoglobulins or complement in the kidney exclusing classical immune complex mechanisms. Although immune complexes have been found in some patients with MCNS (Levinsky et al, 1978).

On immunoflourescent study some times non specific axial arteriolar staining particularly with IgM and complement is seen (Paul et al, 1982). Some cases of MCNS have deposition of IgM which is considered insignificant by pathologists. Deposition of IgG or complement components is absent (Phadke and Bhave, 1990).

Carvallo et al (1981) found in patients of MCNS, no changes by light microscopy or immune flourescence though some times deposits of C_3 and IgM in mesengium were found.

Saxena et al (1988) studied 45 cases of MCNS but IgG, IgM and IgA, C_3 were not seen in any of it, irrespective of their light microscopic appearance.

Mehta and Ali (1985) studied biopsies of 30 patients with nephrotic syndrome by immunoflourescent studies. Eighteen out of 30 cases had MCNS on light microscopy, 10 of these 18, showed no immunoflourescence of kidney tissue. Eight (44%) cases showed coarse to fine granular deposits of IgM (with IgG in 2 and C_3 in one) however, no correlation was found between steroid response and positive immunoflourescence.

Prasad (1977) reported deposits of IgM and occasional mesengial deposits of C_3 in MCNS. In a group of children with IgM deposits, focal segmental IgM deposits were present in approximately 1/3 of both responders and non responders (Mota Hernandez, 1979).

Although it seems certain that some patients with MCNS do have IgM deposits, the clinical and pathological significance of these deposits is yet to be ascertained.

FOCAL GLOMERULAR SCLEROSIS

Immunoflourescent studies show deposits of IgG, C_3 and C_4 complement and fibrin(fibrinogen) within the hyline masses in the sclerotic areas, but non sclerotic areas show either no staining or slight staining with IgM and C_3.

Electron microscopic studies showed diffuse thickening of GBM, partial or complete capillary collapse with presence of focal or diffuse mesengial hypercellularity 2+ to 3+), intercapillary foam cells (60%) and electron dense deposits in basement membrane as well as mesengium. In 7 cases of FSGS studied 5 showed deposits of IgM(only 71.4%) while in 2 cases IgM and C_3 (28.5%).

Membranoproliferative glomerulonephritis

Type-1 showed C_3 deposited in granula pattern and IgG and early complement components (C_{1q} and C_4) are often also present suggesting immune complex pathogenesis. In type II, C_3 is present in irregular granular linear foci in the basement membranes on either side, but no within the dense deposits. C_3 is also present in the mesengium in characteristic circular aggregates (mesengial rings). IgG is often absent and early acting complement components (C_{1q} and C_4) are usually absent from the deposits.

Membranous Nephropathy

Immunoflourescent microscopy shows fine granular deposits of IgG occasionally of C_3 along the GBM.

All 5 cases studied by Saxena et al (1988) showed fine to coarse deposits of IgG and C_3 along glomerular capillary wall, corresponding to electron dense deposits seen subepithelially with the electron microscope.

IMMUNOLOGICAL CORRELATION

Nephrotic syndrome as an immunologically induced disease was first seriously considered in 1907 when Shick, Bell and Clawson produced glomerulonephritis in laboratory animals by injecting either anti whole kidney, anti-glomerular or antibasement serum or by intravenous injection of foreign proteins. Reduced concentration of gamma-globulins in serum of patients with nephrotic syndrome was reported as early as 1940(Longstrom, 1940). Cooper (1967) suggested involvement of complement in a variety of disease processes.

Now it is well known that nephrotic syndrome has a profound effect on the concentrations of several serum proteins. Levels of IgG and transferrin are low while those of haptoglobin, alpha-2 macroglobulin and IgM are elevated. Lewis et al (1971), Giamgiacoma et al (1975), Michael et al (1873). Fragmentary observations have indicated that this this syndrome can also affect the levels of certain complement components.

Because serum levels of individual complement components are helpful in the diagnosis of various glomerulonephritides and in assessing the pathway of complement activation. It is of value to document the effect of a nephrotic syndrome, often present in patients with hypocomplementemic glomerulonephritides, on the complement profile.

The cause of MCNS still remains unclear although several immunologic mechanisms have been postulated.

Shalhoub (1974) stated that exact pathogenesis of minimal change nephrotic syndrome is not known, although several disturbed immunological parameters are found in children.

Some characteristics of disease like association of relapse with seasonal allergies, atopy, low levels of IgG concentration both at the onset and during a relapse suggest that immunological mechanisms do play an important role in its pathogenesis (Thomson et al, 1976).

The clinical association of MCNS with atopy with malignancies such as Hodgkin's disease with known depression of cell mediated immunity, its response to immunosuppressants such as steroid and cyclophosphamide as well as remission induced by measles infection, have given rise to speculations regarding the possibility of immunological abnormalities in the causation of this disease. Depression in cell mediated immunity, abnormalities of immunoglobin synthesis and the association of this syndrome with specific antigens of the HLA system have been described.

A lymphokine that increases vascular permeability (vascular permeability factor) has also been identified in the sera of patients with active disease (Tyrone Mehin et al, 1984).

Decreased delayed hypersensitivity skin responses to PPD have also been reported. Fodar-Petal (1982), Hoyer et al (1982) stated that hypoalbuminemia, hyperlipidemia and zinc deficiency that accompany this disease are known to have depressive effects on cell mediated immunity.

Giangiocoma (1975) observed decreased levels of IgG have been observed in idiopathic nephrotic syndrome irrespective of the course of nephrotic syndrome.

EFFECT OF HUMORAL IMMUNITY

Now it is well known that nephrotic syndrome has a profound effect on the concentration of several serum proteins. Levels of IgG and transferrin the low while those of haptoglobins alpha$_2$ macroglobulin and IgM are elevated.

Studies on the levels of serum immunoglobulins showed significantly lowering of serum IgG associated with proportionate rise in the levels of serum IgM at onset (Giangiocoma et al, 1975; and Glassock et al, 1986; and Sober et al, 1976).

Giangiocoma et al (1975) reported decreased levels of IgG in patients with idiopathic nephrotic syndrome irrespective its course.

Andal et al (1989) reported very low levels of IgG at onset in frequently relapsing children with MCNS, which persisted during remission.

Other reported no significant difference in immunoglobulin levels estimated at onset and at relapse.

Loss of IgG contributed to the reduced serum levels to some extent. However, lowered levels in non proteinuric patients during remission suggested that there is some additional factor accounting for the lowered levels of IgG even after long term remission.

The concentration bears linear correlation.

Groshang et al (1973) noted raised serum IgE in patients with MCNS.

No change in immunoglobulin levels was observed between frequent and infrequent relapsers by Glassock et al (1986).

Selectively decreased titres of serum IgG and IgA with increased or normal titres of IgM have been observed in MCNS by Hoyer (1982) and Tyrone Melvin et al (1984).

Mehta and Ali (1985) studied humoral immunity in a group of 18 patients by measuring IgG, IgM and IgA levels. IgG levels in children with active MCNS was very low. The IgM and IgA levels were within normal limits .

This depression in IgG cannot be explained on urinary losses alone. Increased catabolism may play a part. It has been postulated that the T cell mediated conversion from IgM to IgG synthesis may be defective (Merlan et al, 1982).

Recently decreased in vitro IgG synthesis has been demonstrated in the lymphocytes of patients with MCNS. elevated serum IgE levels have been documented in some patients with MCNS(Schulte-Wissermann et al, 1979).

Higher incidence of atropy in children with MCNS and their first degree relatives as compared to controls was reported by Meadow (1981).

The mean levels of IgM were 303.1±112.4 mg%, 164.0±50.4 mg% and 252.4±76.2 mg% at onset, remission and relapse respectively (Andal, 1989) while mean value of control was 169±89.1 mg%. Sudhir and Yuceoglu (1985) reported the IgM levels to be 65±25 mg% in patients with MCNS type while in controls it was 58±23 mg%.

Yokoyama (1985) reported the mean IgM levels as 267±28, 263±39, 269±41, 234±25, 186±21 and 126±13 mg% in nephrotic syndromes, initial episode, relapse, unstable remission, stable remission and in controls respectively and levels of IgG were reported by Andal et al (1989) as 370.3±201.2, 714.2±374.2, 527.2±299.1 mg% at onset, remission and relapse respectively while it was reported in controls as 1229.2±292.7 mg%.

Gupta et al (1985) reported IgG levels to be 762±209 in nephrotic syndrome with MCNS type while in controls it was 923±256 mg%. Serum IgG was significantly decreased in 7 of 11 patients.

Mehta and Ali (1985) reported serum IgG levels in MCNS group as 576±164.1 mg% while in controls it was 1072±348 mg%.

Yokoyama et al (1985) reported IgG levels as 642±88, 521±110, 891±78, 1051±73 and 1464±86 mg% in initial episode, during relapse, in unstable remission and in stable remission respectively while it was 1276±54 in controls.

EFFECT OF CELL MEDIATED IMMUNITY

The concomittant elevation of IgM with lowering of IgG, may be related to the fact that nephrotic syndrome is primarily a thymic cell dependent immune defect. Cells which normally produce IgM class of antibody before converting to the synthesis of IgG and IgA fail to elicit this response resulting in elevated levels of IgM(Davie et al, 1974 and Eisen, 1973).

Further evidence to support T cell dysfunction comes from studies in which extracts from cultured lymphocytes in 50% of patients with MCNS (Sasadelli et al, 1980), caused enhanced vascular permeability when injected subcutaneously in guinea pigs (Lagrue et al, 1975).

Recently interest has turned to the possibility that MCNS may be related to T cell dysfunction in which humoral factors, perhaps lymphokines are produced which alter glomerular basement membrane permeability (Sasdelli et al, 1980).

This hypothesis is based on observations of spontaneous remissions occurring during the course of measles, or following live measles vaccination (Tuceoglu, 1989), alteration in immunoglobulin levels with elevation of IgM and depression of IgG and the frequent occurrence of nephrotic syndrome in patients with Hodgkin's disease (Long and Hall et al, 1977).

Other immunologic aberrations have also been described such as lymphotoxicity to cell cultured renal

epithelial cells by lymphocytes obtained from patients with MCNS and inhibition of normal blastogenesis by serum from patients with active MCNS (Itika et al, 1979).

MCNS is a disease of unknown etiology. Shalhoub (1979) suggested that MCNS be related to a T cells disorder particularly a disorder of suppressor T cells. Since then a number of studies have suggested multiple immunologic abnormalities in MCNS. Cellular and molecular basis of these defects are not known. Several investigators have reported evidence of a pathogenic role of T cell mediated immunity. Moorolhy et al (1976), Iitaka and West (1979), Minchin (1980) have reported presence of serum inhibitory factor during active stage of disease but lacking during remission.

Studies on T cell subpopulation in children with MCNS have shown not only decreased levels of T helper and suppressor cells but also functional impairment of T helper cells (Sasadelli et al, 1980).

Impaired T cell activity may contribute to the failure of B cells to switch from IgM, synthesis to IgG. Andal et al (1989) showed the functional impairment of T helper cells to persist during remission though quantitative estimation showed a significant rise from the levels at onset.

Taube et al (1981) reported significant lowering of suppressor cell function in children following long

term remission with cyclophosphamide. They observed greater suppressor cell activity in children who continue to relapse even after cyclophosphamide therapy.

Yokoyama (1985) reported that immunological abnormalities in MCNS are characterised by acceleration of the IgE and IgM producing system and impaired maturation of the IgG producing system and impaired maturation of the IgG producing system despite normal differentiation from IgM producing IgG producing system, possibly caused by T cell dysfunction.

Mehta and Ali (1985) assessed cell mediated immunity by absolute T cell count, the blastogenesis index and the skin reactivity to dinitrochlorobenzene (DNCB). There was a significant depression in all 3 parameters.

Steroid administration tended to correct abnormalities of not only T lymphocyte subsets but also of beta lymphocyte subsets and serum. IgG levels. Hereby causing improvement of clinical symptoms.

Disorders of beta lymphocyte function and IgG producing mechanisms who are controlled by T lymphocytes may be involved in the etiology of MCNS and steroid might correct these disorders (Yokoyama et al, 1985).

Chen (1987) reported enhanced suppressor cell activity resulting in increased IgM and reduced IgG production in MCNS children.

EFFECT ON COMPLEMENT SYSTEM

Lange (1960) demonstrated lowering of plasma complement activity after an attack of nephritis. Persistent hypocomplementaemia was observed in cases with membranoproliferative cases. Plasma complement activity was estimated by one of its components C_3 (Klemperer et al (1965). The involvement of complement in a variety of disease processes had been suggested by Cooper (1967).

The measurement of serum levels of specific components of the complement system is helpful in the diagnosis of several forms of chronic glomerulonephritis and in evaluation of therapy.

Prasad et al (1980) studied plasma C_3 complement levels and found hypocomplementemia in 32% of cases initially but on follow up persistently low levels were observed only in 8% and among these 6% had membranoproliferative glomerulonephritis and belonged to low selectivity group. Only one case out of 4 with persistent hypocomplementaemia had high selectivity. Five out of 16 cases with high selectivity were hypocomplementemic.

Since nephrotic syndrome is frequently associated with hypocomplementemic glomerulonephritides, an assessment of the effect of the syndrome per se on level of various components is of importance (Frederic Strife, 1986).

West and Ogg suggested that persistent hypocomplementemia is characteristic of a discrete group of patients with poorly selective proteinuria. None of MCNS had

hypocomplementemia, 3 cases out of 33 had low C_3 levels initially in MCNS group.

Seven out of 8 had low C_3 levels initially in mesengial proliferative group and 3 cases had persistently low levels, while membranoproliferative glomerulonephritis had 5/6 patients initial low levels and 3/6 having persistently low levels. In membranous group, only 1/3 had low levels initially but none had persistently low levels.

Mehta and Ali (1985) reported that serum complement levels are generally normal in MCNS although indirect evidences of complement activation have been reported by Hoyer (1982).

Serum complement levels were never found lower than 85% mg% by Mehta and Ali (1985).

No definite role for circulating immune complexes has been established (Hoyer, 1982).

DEFINITIONS

1. ISKDC Criteria : Generalised swelling, proteinuria $\bar{7}40$ mg/m^2/L, hypoalbuminemia $\underline{<}2.5$ gm%, hypercholesterolemia $\bar{7}200$ mg%.
2. Sharples (1985) defined it as proteinuria at least 3+ on albusfix testing with oedema and a plasma albumin concentration of 25 g/l or less.
3. Meadow et al (1981) : heavy proteinuria 0.05 g/kg/day, serum albumin <25 g/l and variable oedema.

4. O,Koskimies et al (1982) and Saxena et al (1985) : proteinuria $\bar{7}$40 mg/hour/m^2 hypoalbuminemia $\angle$2.5 gm% age within the range of $\bar{7}$12 weeks and $\leq$16 years.

REMISSION

No oedema and urine free of protein by qualitative testing for 5 consecutive days (Rance et al, 1976).

RELAPSE

- Edema or first morning sample of urine contains 2+ reaction for 7 consecutive days (Rance et al, 1976).
- Defined as 3 consecutive days of proteinuria mearuing 2+ or more (Tranin et al, 1975).
- Defined as recurrence of proteinuria 3+ necessitating further steroid treatment.
- Reappearance of proteinuria $\bar{7}$40 mg/hr/m^2 or 2+ or more for 3 consecutive days.

FREQUENT RELAPSERS

- Two relapses within 6 months or three within a year even though they respond to daily prednisolone therapy (Rance et al, 1976).
- Those with four relapses per year or two within 6 months of diagnosis.

RESPONSE

Decrease in rate of urinary excretion of protein to $\angle$4 mg/hr/m^2 for 3 consecutive days (zero to

traces on bed side urine examination).

STEROID RESPONSE

Defined as the abolition of proteinuria within eight weeks of starting treatment with prednisolone with 60 mg/m^2/day or 2 mg/kg/day.

Defined as complete remission within 8 weeks of prednisolone therapy, persisting for an minimum of 2 months after termination of therapy (Tejani et al, 1985).

INITIAL RESPONDER

Any patient who responded during 8 weeks of initial steroid regimen.

NON RESPONDERS TO STEROIDS (Steroid resistant)

A. Early non responder

- Failure to achieve remission with a 4-10 weeks of prednisolone therapy (5-10% of MCNS).
- Any patient who failed to respond during initial 8 weeks of prednisolone therapy (Tranin et al, 1975).

B. Late non responder (5% of MCNS)

Failure to achieve remission with 28 days course of prednisolone after one or more steroid induced remissions. Before labelling the case as non responder, presence of infection is to be excluded (Tranin et al, 1975).

PHASES OF NEPHROTIC SYNDROME

a. Nephrotic phase - Initial episode
- Relapse

b. Remission phase - Unstable remission
- Stable remission.

Unstable Remission

Remission reauiring steroids for maintenance of disappearance of urinary albumin and normal serum albumin.

Stable Remission

Remission maintained despite withdrawal of steroid.

INFREQUENT RELAPSERS

Patients with less than 3 per year or less than two relapses per 6 months.

STEROID DEPENDENT

In these patients proteinuria recurs when dose of steroid is reduced below a critical level or proteinuria occurring within 2 months after termination of treatment on at least 2 consecutive occasions (Rance et al, 1976).

Veda et al (1990) described it as relapse occurring either by reducing dosage of steroids or within 14 days of discontinuing prednisolone.

STEROID RESPONDERS

Those patients who became urine albumin free within 4 weeks of onset of steroid therapy persisting for minimum 2 months after termination of therapy in dosage of 60 mg/m^2/day or 2 mg/kg/day prednisolone.

These were divided into (a) frequent relapsers and (b) infrequent relapsers.

SLOW RESPONDERS

In whom proteinuria becomes less but did not disappear within 8 weeks of steroid therapy though eventually disappears completely (Vaishnav et al, 1983).

FREQUENT RELAPSERS WITH STEROID DEPENDENCY

In whom two consecutive relapsers or 2 out of 4 relapses in any 6 months period occurred after the prednisolone dosage was given for previous relapse had been reduced from daily to intermittent or alternate day schedule or within 14 days of discontinuing a course of steroid therapy (Arbeit gemin Schaft).

Tejani et al (1985) defined it as proteinuria recurring within 2 months after termination of treatment on at least 2 successive occasions.

FREQUENT RELAPSERS WITHOUT STEROID DEPENDENCY

Patients with 2 or more relapses within 6 months of initial response or 4 or more relapses within any 12 months period (ISKDC, 1974).

REMISSION TIMES

Interval from day one without proteinuria to first day of subsequent significant proteinuria.

MEAN RELAPSE FREE INTERVAL

Number of days for which patient remains free from proteinuria.

RESPONSE TIME

Defined as interval between the initiation of treatment and first day of reduction of proteinuria to a negative or trace dipstick reaction obtained for at least 3 days.

REMISSION ON CYCLOPHOSPHAMIDE

Tejani et al (1985) defined as complete loss of proteinuria persisting for at least 6 months. The longer time period for defining a remission on cyclophosphamide as compared to prednisolone is based on the premise that a more toxic drug should be used if greater benefit is derived.

LATE NON-RESPONDERS TO STEROIDS

The late occurrence of steroid resistance cannot be predicted, because various clinical and laboratory features at the onset of nephrotic syndrome as well as the early course in such patients may not differ from those in the larger group who remain steroid sensitive (Srivastava, 1984).

Incidence of late steroid resistance to corticosteroids therapy in patients who initially respond is difficult to estimate because the issue has seldom been addressed. In single report (Trainin, 1975) incidence was 5%. Grupe (1979) suggested it as 4.8%. Srivastava et al (1986) estimated the incidence of late steroid resistance approximately 3%.

Trainin et al (1975) reported 10 patients with late non response to steroids, all with minimal lesions. Of these 7 responded to cyclophosphamide but 5 of them again relapsed.

Occurrence of late steroid resistance is unusual and that such patients have minimal lesions additionally they begin to respond to treatment with cyclophosphamide or chlorambucil and subsequently again become steroid responsive.

Late steroid patients comprise of heterogenous group. Those with focal segmental glomerulosclerosis and resistant to cyclophosphamide therapy may have poor outcome.

TUBERCULOSIS AND NEPHROTIC SYNDROME

Children with nephrotic syndrome are prone to infections. Since tuberculosis is one of the infections commonly seen in children in India, children with nephrotic syndrome may also have or develop tuberculosis. Of 380 cases of nephrotic syndrome, 10% had evidence of

tuberculosis, 34 males and 4 females(Vaishnav et al, 1983). This was four times higher than the incidence of tuberculosis in pediatric age group (2.7%). Children with the age of onset of nephrotic syndrome 7-9 years had higher incidence of tuberculosis as compared to other age groups. 5.4% had tuberculosis earlier and 5.5% developed tuberculosis after the use of steroids. MCNS was biopsy proved in 73.6% cases in tubercular group and 89.5% in non tubercular group.

Response of nephrotic syndrome to steroid in presence of tubercular infection was slow. So any of nephrotic syndrome patient having slow response should be investigated for tuberculosis in addition to other infections.

RECOGNITION OF FREQUENT RELAPSERS

If one is certain about immunopathological mechanisms working in MCNS, one may try and see if there be any differences in MCNS frequent relapser and infrequent relapser. It is known over the course of years that 85% cases of MCNS responded and under go remission on corticosteroid therapy. Of the initial responders 24% do not relapse and 22% get infrequent relapses. However, 53% of responders are frequent relapsers (Grupe, 1979) about 1/3 patients have no relapse or one relapse.

The most difficult problem in case of children with MCNS continues to be occurrence of frequent relapses in patients who respond initially to treatment with steroids. Repeated or continuous administration of steroids

although usually effective is frequently associated with severe toxicity (ISKDC, 1982).

Preventing the occurrence of frequent relapses and until that is possible, finding more effective and safer methods of treating them remains the major unsolved problem in the case of patients with MCNS. Attempts to correlate the course of disease with histologic findings findings have not only with limited success (ISKDC, 1982).

In report of ISKDC (1982) analysis was made of clinical course of 218 responsive children with MCNS during 2 years period following initial response to prednisolone therapy. No correlation was found between the frequency of relapse and :-

1. Histopathologic subgroups of MCNS.
2. Clinical and laboratory characteristics observable at the time of diagnosis.
3. The time of initial response.
4. Interval between initial response and first relapse.

CLINICALLY

Number of relapses that occurred during first 6 months was highly predictive of the subsequent course of 99 children who had no relapse during first 6 months, 93 had fewer than 3 relapses during subsequent 18 months and only one had more than 6 relapses. In contrast, 37 cases who had 3 or more relapses during first 6 months, 17 had $\bar{7}6$, 13 had $\bar{7}10$ and only 7 had $\angle 3$ relapses. So it

proves that course of nephrotic syndrome during first 6 months can predict the likely course regarding identification of frequent relapsers.

ISKDC (1982) : Absence of relapse during first 6 months following the initial response proved to be an excellent clinical predictor of a favourable course during first 2 years. In contrast, occurrence of 3 or more relapses during initial 6 months period can be used clinically to predict and frequently relapsing course. Fifty percent of children who had 3 or more relapses in first 6 months will continue to have frequent relapses.

Contrary to reports by Cornfield and Stewartz (1966), Arneil and Lam (1966) Seigel et al (1972), presence of hematuria, transient azotemia or hypertension at the time of diagnosis did not correlate with the frequency of relapses during first 2 years.

HISTOPATHOLOGICALLY

ISKDC (1982)

Presence of either mild mesengial proliferation or focal tubular changes on renal biopsy is associated with a decreased rate of initial response but not with an increased frequency of relapses. At present therefore potential frequent relapsers cannot be identified from histopathological characteristics.

Saxena et al (1985) after studying clinical feature and correlating them with histopathological examination inferenced that majority of patients having

mesengial alterations like mild mesengial thickening, mild mesengial hypertrophy and focal glomerular obsolescence belong to non responders, steroid dependent and frequently relapsing group.

ISKDC (1981) divided minimal lesions on light microscopic examination into 5 subtypes and tried to correlate these subtypes with steroid response:

1. Nil diseases.
2. Minimal mesengial thcikening.
3. Focal glomerular obsolescence.
4. Focal tubular changes
5. Minimal mesengial hypercellularity.

A higher proportion of initial non responders were among group with focal tubular changes and minimal mesengial hypercellularity. There was no difference in number of frequent relapses in each group.

IMMUNOLOGICALLY

Andal et al (1990) described differences in IgG and IgM in frequent relapsers and infrequent relapsers. Levels of IgG were significantly low and IgM high in frequent relapsers and remained so in remission as compared to infrequent relapsers. Thus persistently low levels of IgG may be a pointer towards frequent relapser, children with frequent relapsers were found to having very low IgG levels at onset.

Some groups have shown high mesengial cellularity and immune complex deposits in frequent relapsers. So low IgG and abnormal histology, immunopathology may indicate that the patients could be a frequent relapser.

Giangiocoma (1975) and Glassock (1986) reported no change in immunoglobulin levels between frequent and infrequent relapsers.

According to study by Andal et al (1990) very low levels of IgG at onset may serve as a marker for early identification of frequent relapsers.

SYMPTOMATOLOGY

Age of onset

Sixty percent of the cases of MCNS variety fall between 2-6 years of age. Though it is reported before 1 year and adult age. In a study by Saxena et al (1988), mean age of onset for MCNS was found 5.899±3.462, 9.857± 2.795 years for FSGS, 9.556±1.740 years for membranoproliferative glomerulonephritis and 7.600±1.949 years for membranous nephritis. Sixty six children studied in this group showed mean age of 7.5 years at the time of initial presentation.

Saxena et al (1988) reported definite male dominance (3 : 1).

Paul and Enery (1982 : Though nephrotic syndrome can present at any age but 74% of children with MCNS have onset of their disease between 2-7 years with a male :

female ratio of 2:1. In adolescence and adults, this sex ratio is almost 1 : 1.

Rance et al (1976 : Most children with MCNS present between : 1 and 6 years of age. Earlier onset of nephrotic syndrome especially under 3 months of age, is more likely in patients with underlying disease. Male : female ratio is 2 : 1. While focal glomerular sclerosis can present at all ages. Male to female ratio was 3 : 2 (Habib et al, 1972).

In MPGN lesion usual age of onset was found to be between 6-16 years. female to male ratio was 1 : 1. It is commonest lesion in second decade of life (Habib et al, 1972).

In membranous nephropathy usually the patients were between 1 to 14years of age. Male to female ratio was 3 : 1. It was the most common cause of nephrotic syndrome in adults(Habib et al, 1972). In nephrotic syndrome due to post streptococcal glomerulonephritis, age of onset was usually after 3 years. i.e. school going age.

EDEMA

This is the commonest presentation of nephrotic syndrome. Edema is soft pitting, usually starting as periorbital and slowly progressing to dependent parts of body and then generalized. In its course ascites and pleural effusions usually occur. Edema can be periorbital pretibial, pedal, anterior abdominal wall, scrotal,or labial involving perineum.

Periorbital swelling is more prominent in the morning, subsiding throughout the day. Whereas ankles become progressively was more common. Facial swelling can be misdiagnosed as allergic reaction and weight gain due to edema can be falsely interforated as a sign of good health. Edema is the hall mark of presenting features of nephrotic syndrome.

Oedema formation was defined by Bohlin (1984) as weight gain during 3 days preceding the study and more than 0.6% weight gain of the body weight per day.

OLIGURIA

Oliguria is presenting complaint, usually along with edema. It is due to hypovolemia which is in turn due to fall in plasma oncotic pressure due to loss of albumin. Urine is opalascent due to lipiduria.

HEMATURIA

Gross hematuria is quite rare in minimal lesion of nephrotic syndrome. It was reported in 13% of MCNS cases by White (1971).

Gross hematuria is rare in MCNS though it can be present microscopically (Habib et al, 1973).

Habib et al (1973) reported microscopic hematuria in 66% cases of FSGS, 68% in MPGN while gross in 20% while in 70% cases of membranous nephropathy while 20% of these patients presented with gross hematuria.

Microscopic hematuria was reported to occur in 13 to 29% at the time of diagnosis by Lagrue et al(1975)

and habib et al (1971), while gross hematuria was reported to be in only 1.4% of cases. Saxena et al (1988) showed presence of hematuria in 40% patients among non responsives. Microscopic hematuria is commonest in patients with FSGS and is presenting feature in 50 to 90% of cases (Cameroon, 1966; 1973; Glassgow, 1971). Bohlin (1984) reported that none of their 23 patients of MCNS had persistent hematuria.

HYPERTENSION

It is uncommon in idiopathic nephrotic syndrome It was reported in 9% cases by White (1971). It is present in 6-13% children with MCNS and usually mild and normal (ISKDC, 1982). Habib et al (1973) reported hypertension in 10% cases of FSGS in 25% in MPGN and in 5% cases of membranous nephropathy.

Saxena et al (1988) reported hypertension in 35.5% cases of non responding type. Majority of the patients presented with headache, swelling, nausea, vomiting and poor appetite.

Sonja Kuster et al (1990) reported that in MCNS 95% of children with nephrotic syndrome had hypertension prior to steroid treatment in edematous phase(B.P. 795% percentile of age). After complete remission, the prevalence of hypertension decreased to 19%. In FSGS prevalence of hypertension was 91% and 24% after remission.

They concluded that irrespective of age, hypertension is a common feature of nephrotic syndrome unrelated to steroid therapy or renal failure.

Bohlin et al (1984) studied 23 children aged 2 to 15 years of MCNS(Biopsy proved 21) and reported none of them had hypertension.

AZOTEMIA

Saxena et al (1988) reported azotemia in 28% cases of idiopathic nephrotic syndrome.

DIARRHOEA AND ABDOMINAL PAIN

Diarrhoea and abdominal pain is usually present in intestinal wall oedema and requires no treatment.

DIFFERENTIATION OF MCNS FROM OTHER ASSOCIATED DISEASES WITH NEPHROTIC SYNDROME

Early differentiation of patients with MCNS from those nephrotic syndrome associated with focal glomerular sclerosis or other forms of chronic or acute nephritis is of prime importance.

Manifestations that favour a diagnosis of MCNS are absence of azotemia, hypocomplementemia, hypertension, hematuria and age 1 to 6 years. These features, except for hypocomplementemia may be found in 10-20% of children with MCNS (Habib et al, 1971; ISKDC, 1978 and White, 1970).

These features are much commoner, especially when present in combination, in patients of nephrotic syndrome caused by other than MCNS.

Even though these clinical features may be helpful the most accurate and non-invasive discriminator of glomerular disease causing nephrotic syndrome is the child's

initial response to intensive treatment with prednisolone (ISKDC, 1978; White, 1970, ISKDC, 1981).

Of the total 471 nephrotic syndrome patients who responded to prednisolone, 92% had MCNS proved by renal biopsy (ISKDC, 1981).

Ninety three percent cases of 363 patients proved to be MCNS by biopsy among those who responded to initial 8 weeks of prednisolone treatment with complete loss of proteinuria.

Clinical features that suggest the syndrome may be due to a histologic lesion other than MCNS include :

1. Children less than 9 months of age.
2. Persistent hematuria.
3. Heme or red cell casts in urine.
4. Low serum complement.
5. Azotemia

In absence of these signs, it should be assumed that child is having MCNS (Cameroon, 1968).

LAB DIAGNOSIS

24 hour and bed side urinary protein analysis

Urine normally contains small amount of protein however, sensitivity of standard diagnostic test is adjusted so that this is not detected.

Nephrotic syndrome is characterized by massive proteinuria and nearly all clinical and biochemical changes are due to such heavy proteinuria. It is the single most diagnostic laboratory finding in patients with nephrotic syndrome.

The upper limit of normal proteinuria in children is not well defined, but is probably in the order of 100 mg/m^2/hour.

Protein excretion in excess of 200 mg/day is definitely abnormal either in child or an adult.

Abramonicz et al (1970) : ISKDC defined nephrotic proteinuria as $\geq$40 mg/m^2/hour.

Degrees of proteinuria (Honser, 1984 and ISKDC, 1981).

Physiologic	$<$0.1 g/m^2/day
Intermediate	$\geq$0.1 and $<$1 g/m^2/day
Nephrotic	$\geq$1.0 g/m^2/day

Cameroon (1968) and James defined massive proteinuria as urinary protein exceeding 50-100 mg/kg/day.

Saxena et al (1988) found that 60% patients under 6 years of age (mean 5.8 years) of MCNS presented mainly with proteinuria.

Bed side diagnosis of massive proteinuria is made by 4+ reaction by heat acetic acid test.

PROTEIN SELECTIVITY INDEX (SPI)

SPI is defined as the ratio of urine to serum concentrations of a large molecular weight. Serum protein (IgG or transferrin) divided by simultaneously measured ratio of urine to serum concentration of albumin multiplied by 100.

$$SPI = \frac{\text{Urine IgG/Plasma IgG}}{\text{Urine albumin/plasma albumin}} \times 100$$

This technique defines the relative permeability of the GBM to serum proteins of different molecular weights when the proteins of larger molecular weight pass the glomerular filter, the higher is the SPI, worst is the prognosis. In MCNS, SPI remains <4. In membranous and proliferative nephropathies SPI is usually more than 0.2 and predicts a poor response to steroids and guarded prognosis.

Serum Albumin

Marked hypoalbuminemia is one of the major characteristics of nephrotic syndrome with serum albumin usually <2.5 gm% or low.

Serum Cholesterol

This is considered when serum cholesterol levels are more than 200 mg%. From the practical stand point, plasma cholesterol levels become elevated as serum albumin concentrations drop below 3 g% and of triglycerides when serum albumin falls below 1 gm% (Baxter et al, 1960).

Blood Urea and Serum Creatinine

Elevation of serum creatinine and blood urea nitrogen are initially present in approximately 25% of children with MCNS (White et al, 1970; ISKDC, 1978).

Saxena et al (1988) reported that 28% cases of idiopathic nephrotic syndrome had azotemia.

URINE OSMOLALITY

Patients with nephrotic syndrome had impaired concentrating capacity evidenced by low urinary osmolaoity. Serum albumin levels do not affect urine osmolality. But patients with clinically severe disease had more severe impairment of urinary concentrating capacity (UCC). Normal levels of urinary osmolality after an overnight fast is 800-1300 m Osm/kg.

Date and Kaushik et al (1990) reported severe impairment of UCC in patients with clinically severe disease i.e. frequent relapses. They reported urine osmolality 432.18±125 (115-690) while in controls it was 798.5±81.7 (710-960).

DIAGNOSIS OF NEPHROTIC SYNDROME

It was made on basis of characteristic clinical history of oedema, laboratory findings of heavy proteinuria more than 50/kg/day or more than 40 mg/m^2/hour hypoalbuminemia ⟨2.5 gm% and hypocholesterolemia ⟨200 mg%.

Diagnosis of steroid responsive nephrotic syndrome was made on basis of absence of contradictory features like hypertension, persistent hematuria, persistent azotemia and hypocomplementemia. ISKDC laid down following criteria for selection of patients of idiopathic nephrotic syndrome.

1. Heavy proteinuria ⩾40 mg/m^2/hour determined quantitative on 24 hour urine collection.

2. Hypoalbuminemia $\leq$2.5 gm%.

3. No evidence of underlying systemic disease or exposure to agents known to be associated with nephrotic syndrome.

4. Age $\geq$12 weeks and $\leq$16 years at the time of diagnosis.

MANAGEMENT

Steroids

Steroids are the mainstay of treatment of idiopathic nephrotic syndrome. Various regimens are being followed for the treatment of nephrotic syndrome.

Long term daily therapy

Initial dose of prednisolone 2 mg/kg/day in divided doses for 1-3 months followed by a tapering dose schedule during 3-6 months by decreasing the dose by 5 mg/day on alternate day.

ISKDC (1976)

a. To induce remission (daily prednisolone therapy) : 20 mg/kg/day (maximum 80 mg/day) in 3-4 divided doses until the urine is protein free for 5 days (maximum duration of 28 days), if remission does not occur within 28 days intermittent therapy is started at 4 mg/kg (maximum 120 mg) with break fast upto 28 days on alternate days.

b. To maintain remission (Intermittent therapy):

i) 2.0 mg/kg/day (Maximum 80 mg) with breakfast on

alternate days for 28 days. It is then gradually reduced over 2-4 months by 10 mg decrements to 30 mg and then by 5 mg decrements until discontinued.

ii) 2 mg/kg/day in 3-4 divided doses on 3 consecutive days each week for 4 weeks. It is then gradually reduced over 2-4 months until discontinued.

Standard intermittent therapy :(ISKDC, 1979)

Start the initial dose of prednisolone 60 mg/m^2/day (maximum 80 mg) in divided doses daily till remission is obtained then 40 mg/m^2/day of prednisolone given in divided doses on 3 consecutive days out of 7 for a period of 4 weeks.

Short term daily therapy(Arbeits geinmeischaft, 1981):

Initial regimen with 60 mg/m^2/day immediately after remission treatment with prednisolone was discontinued.

Standard alternate day therapy(Brodehl et al, 1982) :

Start initial dose of 60 mg/m^2/day in divided doses till remission is obtained then 40 mg/m^2/day as single morning dose alternate day for 4 weeks.

ISKDC (1982)

Initial treatment - 60 mg/m^2/day maximum dose 80 mg/day in divided doses for 4 weeks followed by 40 mg/m^2/day in divided doses for 3 consecutive days out of 7 for 4 weeks. Treatment of relapse is the same.

Srivastava et a

Start with prednisolone 2 mg/kg/day in 4 divided doses for 4 weeks followed by same dose alternate day for another 4 weeks.

Each relapse to be treated with 2 mg/kg/day prednisolone until proteinuria abolished maximum for 4 weeks followed by same dose alternate day for 4 weeks.

Veda et al (1990)

Initial episode of the nephrotic syndrome were treated with prednisolone in divided doses of 60 mg/m^2/ day for 4 weeks with the dose being tapered by 5-10 mg/ m^2/ every two weeks during next 3-4 months.

Those patients who had milder degrees of proteinuria (74 mg/m^2/hour but <40 mg/m^2/hour) were managed with previous maintenance dose of prednisolone for 1-2 weeks, the dose either being increased to 60 mg/ m^2/day if remission (<4 mg/m^2/hour proteinuria) was not achieved.

Patients who respond to initial prednisolone medication with two consecutive days of protein free urine have their regimen of prednisolone switched to an alternate morning schedule of 2 mg/kg alternate morning schedule maintenance dose is continued for 1 month and then decreased to 1 mg/kg for a second month and finally decreased and discontinued in third month of follow up. (ISKDC, 1982).

Srivastava et a

Start with prednisolone 2 mg/kg/day in 4 divided doses for 4 weeks followed by same dose alternate day for another 4 weeks.

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Treating a relapse

Follow up alternate morning prednisolone is continued in a slow decreasing dosage over 6-12 months before being discontinued. Alternate day regime is reported to be more effective in preventing disease relapse and has less steroid toxicity in comparison to intermittent regimen suggested by ISKDC.

Some workers of German pediatric nephrology group recommended a low dose prednisolone 35 mg/m^2/day every alternate day for 40 weeks after response is induced by 60 mg/m^2/day initially in a frequently relapsing patient. Alternate day therapy with low dose keeps patient free of relapses and also minimises steroid toxicity.

Feehally and Kendall defined MCNS as steroid responsive nephrotic syndrome (complete abolition of proteinuria within 4 weeks in response to corticosteroid treatment) with no hypertension or renal impairment. In some cases there was further information from percutaneous renal biopsy.

Siegel et al (1987) reported that frequently relapsing steroid responsive childhood nephrotic syndrome is assumed to have MCNS morphology based on clinical course. It has been reported that frequently relapsing children maintained on alternate day regimen relapsed less often than those treated for 3 consecutive days per week. How a difference in the maintenance regimen might have

affected the results reported cannot be determined. (Arbeissgemenschaft Fini, Pediatriascha Nephrolgie, 1981).

An early frequently relapsing course should not be considered an automatic indication for instruction of treatment with drugs other than prednisolone. Since 50% of patients having 3 relapses in first 6 months had relatively few relapses in subsequent 18 months and those who did relapse frequently showed little or no evidence of steroid toxicity a alternate day regime.

Rance et al (1976) reported alternate day method cause less cushingoid obesity and hypertension.

Polito et al (1986) reported that alternate day regimen did not affect statural growth and bone maturation of children with lipid nephrosis. Only one of 20 children treated for 1 year last 0.5 SD.

Rees (1990) suggested that alternate day treatment may minimize growth retardation and leave final height unaffected.

It has been observed that when a patient responds to corticosteroids initially, he would generally continue to do so even if he is a frequent relapser. He may become steroid dependent but over all he responds to steroids every time he gets a relapse.

Uncomplicated child with nephrotic syndrome who is over the age of 1 but under the age of 7 years, has a normal C_3 concentration and does not have gross hematuria,

probably has MCNS and should be given a therapeutic trial with prednisolone. If histologic diagnosis is one of proliferative forms of disease, membranous nephropathy, or advanced glomerular sclerosis, steroid therapy appears to be ineffectual and may cause hypertension or other complications. Children with age 7 and 6 years having gross hematuria and hypertension are more likely to have disease other than MCNS.

ISKDC has shown that all nephrotic children who are going to respond to prednisolone 73% did so within 14 days and 94% within 28 days of initiation of the daily divided dose.

In patients who at the end of 4 weeks are still nephrotic or still have 1 to 2+ amounts of proteins renal biopsy should be performed. Within these criteria very few children with MCNS will need a renal biopsy.

MANAGEMENT OF CHILDREN WITH FREQUENT RELAPSES/STEROID DEPENDENCE

Twenty five percent of MCNS exhibit frequent relapses (ISKDC, 1974). In such patients, treatment line is controversial use of alkylating agents is recommended in such cases by Clim et al (1973), Garin et al (1978), Grupe et al (1973). But there are potential side effects of such agents and visual long term prognosis in patients with MCNS. Paul and Eneny (1982) attempted to suppress relapses with long term alternate day prednisolone.

Maintenance with 1.4 mg/kg alternate day of prednisolone is usually not associated with significant steroid toxicity and is acceptable alternative to use of alkylating agents.

ROLE OF CYCLOPHOSPHAMIDE

Adequate controlled trials have shown that cyclophosphamide used in combination with steroids will decrease the rate of relapse in children who have steroid responsive frequently relapsing syndrome.

Usual regimen is 2 to 3 mg/kg/24 hours for 8 weeks. Sixty five percent patients remain in remission after 5 years of treatment. Permanent remission was reported in 50% cases. Response to cyclophosphamide may be predictable from the pattern of response to steroid therapy. Of those who relapse immediately after tapering steroids, 2/3rds also relapse quickly after cyclophosphamide is also true.

Cyclophosphamide used in combination with steroids will decrease the rate of relapse in children who have steroid responsive frequently relapsing syndrome (Seigel et al, 1981).

Tejani et al (1985) studied efficacy of cyclophosphamide in 39 steroid sensitive frequently relapsing nephrotic syndrome. It was used due to heavy steroid dependence and steroid toxicity. Hundred percent of patients with MCNS responded to cyclophosphamide but only

1 of 15 FSGS patients responded. They suggested that cyclophosphamide should not be used in patients whose disease has evolved from MCNS to FSGS.

Ueda et al (1990) treated 32 patients with cyclophosphamide for 8 weeks and 41 for 12 weeks. The relapse free rate of patients treated for 8 weeks (25%) was similar to that of treated for 12 weeks (24%). They conducted that cyclophosphamide should no longer be used longer than 8 weeks at a dose of 2 mg/kg/day in children with MCNS.

Moncrief et al (1969) and Chiu et al (1973), in well controlled trials showed high dose leukopenic regimen combined with low dose prednisolone is effective in reducing the frequency of relapsing disease and lengthening the interval between relapses of proteinuria.

Following 90 day course 75% children did not have a relapse within 1 year of treatment and 50% did not relapse for 2 years.

Paul and T. Mc Enery (1982) suggested 2.0 to 2.5 mg/kg/day in conjunction with small daily dose of prednisolone for 8-16 weeks.

Alopecia, leukopenia, hemorrhagic cystitis, infection have to be looked for it also affects gonadal function.

CHLORAMBUCIL

Clinical trials with chlorambucil are recent.

It has advantage of fewer toxic side effects and fewer relapses when compared to cyclophosphamide.

Grupe et al (1976), Baluarali (1978) and Callis et al (1980) recommended the dose 2 mg/kg/day for 5-15 weeks in combination with low dose prednisolone. This yeilded continuous remission rate in 95% children, 1 year after combined therapy and in 85% after 3 years combined therapy (Williams et al, 1980).

Seizures was a a problem but other toxic effects of cyclophosphamide were less.

MANAGEMENT OF STEROID RESISTANT MCNS

It carried a poor prognosis and 80% progress to end stage renal disease.

Ciclosporin

It is a powerful immunosuppressive agent. (Patrick Niaudet (1991) suggested that ciclosporin in combination with prednisolone may be efficient in patients with steroid resistant nephrotic syndrome with either MCNS or FSGS.

Dose recommended is 150-200 mg/m^2/day combined with daily prednisolone 30 mg/m^2 for 1 month and with alternate day prednisolone 30 mg/m^2 thereafter for 5 months.

Meyrier et al (1986) showed cyclosporin-A may be effective in treatment of patients with nephrotic syndrome that resist every other form of treatment and especially in those with lipoid nephrosis.

Peter Hoyer (1980) reported that cyclosporin was effective in MCNS patients resistant to steroids and cyclophosphamide, in severe steroids dependent MCNS. Dosage administered were 100-200 mg/m^2/day along with alternate day. They found that relapse rate reduced considerably and even resistant cases responded.

Though its extensive use is still not done, caution trials are recommended.

MANAGEMENT OF PATIENTS WITH MESENGIAL PROLIFERATION NEPHROTIC SYNDROME

2.3-5.3% of patients of nephrotic syndrome will have this lesion on renal biopsy. Clinically these patients are not distinguishable from MCNS. Mean age and older and incidence of macro-microscopic hematuria is higher (36-100%). Fifty percent respond to usual steroid therapy and 25% to immunosuppressive therapy.

MANAGEMENT OF FSGS

Importance of this lesion is, relative corticosteroid resistance and progression to end stage renal disease as described by Churg et al in report for ISKDC (1970). Seventeen percent of biopsy proven FSGS patients respond to steroids but usually have frequent relapses. This group comprise 40% of all cases which are steroid resistant (Nash et al, 1976). Modes of treatment are azothiaprine, dipyridamole, aspirin.

Steroid resistance cases have poorer prognosis.

Overall 50% survive from 3 to 16 years.

MANAGEMENT OF OEDEMA

Diuretics are not indicated unless ascites or pleural effusion are distressing to the patients. Major complication of diuretic therapy is hypokalemia.

a. Salt restriction : Salt should be restricted to 0.5- to 1 gm/day till oedema subsides.

b. Salt poor albumin : 0.5-1 g/kg over 60 minutes followed by I/V furoscemide.

HYPERTENSION

Following diuresis, blood pressure usually becomes normal. Otherwise hydrallazine can be used intravenously or oral 0.7 mg/kg/day in 4 divided doses. Intravenous diazoxide in acute emergency, it can be increased to 200 mg/day.

SUPPORTIVE CARE

- Normal ambulation should be maintained.
- Infections should be treated accordingly.
- No dietary restriction except low salt diet is indicated in uncomplicated case.

MATERIAL

AND

METHOD

MATERIAL AND METHODS

The present study was conducted in the department of Pediatrics, M.L.B. Medical College, Hospital, Jhansi, over a period of two years from August, 1991 to July, 1993. The study was primarily aimed to study the clinical as well as immunological profile of nephrotic syndrome in Bundelkhand region.

Accordingly on the basis of history, general and systemic clinical examination, investigations, all cases of nephrotic syndrome admitted in Pediatric ward and attending Pediatric OPD formed the basis of present study.

CLINICAL DIAGNOSIS

History

A detailed present, past and relevant history was recorded in each and every case. Typical present history in a classical case was that of generalized swelling, usually starting as puffiness of eyes, particularly noted in the morning and history of low output of urine. History of gross hematuria, headache, nausea and vomitings was asked in each case.

History of infections, particularly pyoderma, upper respiratory tract infections, malaria, drug intake was also obtained.

Age, sex, family history, history of any underlying systemic disease, allergies were recorded in each case.

Past history was ellicited in each case so that full account of relapses and remissions could be known.

PHYSICAL EXAMINATION

A thorough general and systemic examination was conducted in each and every case and findings were recorded on the predesigned proforma. During general examination emphasis was given to ellicit oedema whether pedal, anterior abdominal wall, scrotal, periorbital. Signs of steroid effect and blood pressure were carefully monitored in each case.

In examination of respiratory system especially evidence of hydrothorax was searched in each case. In examination of abdomen, ascites, hepatosplenomegaly, anterior wall oedema were carefully looked for. Kidneys were palpated for any renal anomaly and renal angles were examination. Cardiovascular and central nervous system was watched carefully.

Children were examined for evidence of any multi-system disorders like S.L.E., Rheumatoid arthritis, Henoch Schonlein purpura, Sjogren's syndrome, tuberculosis etc. which may provide some etiological clue to the disease process.

LAB. DIAGNOSIS

After taking a detailed history and doing a thorough examination, following investigations were performed.

Urine

a. Bed side urine examination for albumin : By heat and acetic acid test was performed regularly and also taught to the parents of the patients.

Interpretation :

- \- No cloudiness,
- ± cloudiness barely visible (traces)
- \+ Definite cloudiness, no granularity/clocculation.
- ++ Granular cloudiness. No flocculation(0.1% protein).
- +++ Dense opaque cloud, clearly flocculated (0.2 - 0.3% protein).
- ++++ A thick/almost solid precipitate (7 0.5% protein).

b. Sugar : By benedicts qualitative glucose test.

c. Microscopic : Clean fresh morning mid stream sample was collected and centrifuged and examined for R.B.C's, pus cells, casts, epithelial cells.

d. Specific gravity : Specific gravity was measured by urinometer.

e. Quantitative estimation of protein in urine :

- Urine collection : Child was asked to void the bladder and urine was collected in a clean large bottle for next 24 hours.
- 24 hour urinary protein was estimated by Esbach's albuminometer.

- Massive proteinuria was defined as excretion of 40 mg or more per m^2 of surface area or 750 mg/kg/day.

2. Routine Blood Examination

Total leucocyte count (TLC), differential leucocyte count (DLC) by Newbaur's chamber, diluting fluid used, turk's solution were done to rule out underlying systemic or acute infections. ESR by Wintrobe's method and hemoglobin estimation was also done in selected cases.

3. Blood Urea : It was estimated by Nessler's method.

4. Serum Cholesterol : It was estimated by routine method of Wybenga et al using photocolorimeter.

5. Serum Creatinine : It was also estimated by photocolorimeter.

6. Serum Proteins : Serum proteins were estimated by Reinhold method and serum albumin by Biuret's method.

7. Radiography : Skiagram chest PA view was done in cases suspected of having primary complex.

DIAGNOSIS OF NEPHROTIC SYNDROME

After conducting thorough clinical examination and investigations cases were diagnosed on basis of criteria laid down by international study of kidney diseases in children (ISKDC) viz.

a. Generalised swelling.

b. Proteinuria 740 mg/m^2/hour determined qualitatively on 24 hour collected urine sample or 750 mg/kg/day.

c. Hypoalbuminemia /2.5 gm serum albumin.

d. Hypercholesterolemia 7200 mg% serum cholesterol.

HISTOPATHOLOGIC METHODS

As most of the cases of minimal change nephrotic syndrome respond to usual steroid therapy and most of the cases not responding to steroid therapy are not MCNS type, renal biopsy was performed to only in steroid resistant or frequent relapses or steroid dependent or age more than 7 years or presenting with gross hematuria and hypertension, so that underlying pathology of the lesion could be underlined. Cases were carefully followed up to study the progress of disease following therapy before they were labelled as steroid resistant, dependent or frequent relapses. Renal tissue was obtained by percutaneous biopsy performed under local anaesthesia by trucut needle(travenol). Biopsy was fixed in formaline and tissue processed in autotechnicon. Paraffin imbedded blocks were prepared and sections were cut at 5 u thickness by microtone. Staining was done by H & E technique. Slides were made and studied under light microscope. The changes which were especially looked were cellular proliferation, glomerular basement thickening (seen by staining with PAS e.g. in membranous glomerulopathy) and focal sclerosis of gromeruli.

IMMUNOLOGICAL METHODS

Quantitative determination of individual serum immunoglobulins (IgG, IgM) was done by Radial Immuno diffusion by Fahey and Mckelvy technique.

Collection of Sera

Serum was separated from blood samples and stored in sterile vials in refrigerator. Samples were drawn both in nephrotic and remission phase.

Gel Diffusion Procedure

Three wells in agar plate were filled with 3 dilutions of reference standard 100%, 50% and 25%. Remaining 9 wells of plate were filled with 9 serum samples in which estimations were to be carried out. Care was taken not to underfill or over flow the wells. It was precisely filled to the brim by using capillary tubes or by syringe with 26G needle.

Plate was left for development of precipitin ring in inverted position (only after lid of plate was replaced and kept aside for 10 minutes). Plate was left for IgM for 24 hours at room temperature and another 24 hours at $4^{\circ}C$ and for IgG over night for 18 hours at room temperature. During this period immunoprecipitate was formed. Each individual antigen produces a single precipitin line, locations of which depends upon the rate of diffusion and concentration of antigen. Diffusion rate of protein depends upon molecular weight.

Higher molecular weight globulin are precipitated in proximity of point of application. Low molecular weight proteins are precipitated nearer to antibody well.

Immunoprecipitation rings are carefully measured and standard graph is contructed using values of reference standard (Standard curve). Semilog graph paper was used to draw graph. Diameter of rings is plotted on linear scale while the quantitative value (100%, 50% and 25%) was plotted on log scale. The values of unknown samples were found out directly by interpolation on standard graph.

Statistical Methods

Statistical significance was assessed by student 't' test.

FOLLOW UP OF CASES

Patients were put on steroids and followed up. On the basis of results and clinical examination they were grouped as follows after careful follow up.

A. Steroid responders.

B. Steroid dependent.

C. Non responders to steroids.

A. STEROID RESPONDERS

Those patients who became urine albumin free within 4 weeks of onset of steroid therapy, persisting for minimum of 2 months after termination of therapy in dosage of 60 mg/m^2 or 2 mg/kg/day Prednisolone. These were again divided into :

a. Frequent Relapsers

Those patients who had 2 relapses within 6 months or 3 relapses in a year even though they responded to prednisolone therapy.

b. Infrequent relapsers : Less than 3 per year or ⩽2 per 6 months.

B. STEROID DEPENDENT

In these patients proteinuria recurred when dose was reduced below a critical level(when put on alternate day regime) or proteinuria occurring within 2 months after termination of treatment on at least 2 successive occasions.

C. NON RESPONDERS TO STEROIDS

a. Early non responders : Failure to achieve remission with a initial 28 days course of prednisolone.

b. Late non responders : Failure to achieve remission with 28 days course of prednisolone after one or more steroid induced remissions. Before labelling as non responders, presence of infection was carefully excluded.

According to disease activity patients were placed in following phases :

i) Nephrotic Phase :
- Initial episode
- Relapse.

ii) Remission Phase :

- Unstable remission : Remission requiring steroids for maintenance of dissappearance of urinary albumin and normal serum albumin.
- Stable remission : Remission maintained despite withdrawal of steroid.

DEFINITIONS

Remission : No oedema and urine free of protein by qualitative testing for consecutive 5 days.

Relapse : Oedema or first morning sample of urine contains 2+ reaction for 7 consecutive days.

OBSERVATIONS

O B S E R V A T I O N

The present study was conducted in the department of Paediatrics, M.L.B. Medical College, Hospital, Jhansi over a period of two years from August, 1991 to July, 1993. The main aim of this study was to evaluate the clinical as well as immunological profile of nephrotic syndrome in children of this region.

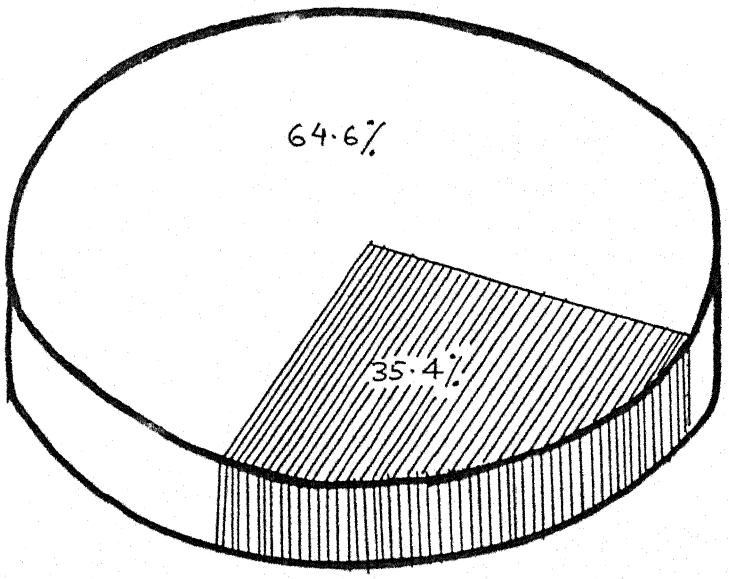
The incidence of nephrotic syndrome of total paediatric admissions in this study was observed to be 1.62%. Nephrotic syndrome comprised of 72.2% of children presenting with renal diseases in this duration in our hospital.

Table I depicts the sex distribution of nephrotic syndrome in present study. There was 42 males (64.6%) and 23 females (35.4%) in our study. Male : female ratio was observed to be 1.8 : 1.

TABLE I : Sex distribution of disease (N=65).

Sex	No.of cases	Percentage
Male	42	64.6
Female	23	35.4
TOTAL	65	100.0

None of the sibs or members of the family of present study group were found to be suffering from nephrotic syndrome.



1.8 : 1

Fig. : MALE FEMALE RATIO.

Table II shows the number of patients which presented in various age groups. Majority (27) of cases (42.53%) were observed in the age group of 4-6 years. This was followed by age group 1-3 years (15 cases) i.e. 23.08%; then 7-9 years, 12 cases (18.46%) and then 10-14 years group, 9 cases (13.85%). Least cases fell below the age of 1 years (3.08%). Thus approximately two thirds (64.61%) cases were between the age of 1 to 6 years. Mean age observed in this study was 5.8 years.

TABLE II : Age of onset (N=65).

Age in years	No.of cases	Percentage	
∠ 1	2	3.08	
1 - 3	15	23.08	64.61%
4 - 6	27	41.53	
7 - 9	12	18.46	
10 - 14	9	13.85	
TOTAL	65	100.00	

TABLE III : Stage of disease in which patient was first seen. (N=65).

Group	Phase	No.of cases	Percentage
A	Initial episode	42	64.61
B	Relapse	23	35.39

Table III depicts the stage of disease in which patient came into our contact for the first time. It was

observed that 64.61% cases never had similar episode before, while 35.39% cases were in stage of relapse.

TABLE IV : Profile of common presenting symptoms.

Symptoms	Group A(N=42) Initial episode		Group B(N=23) Relapse		Total (N=65)
	No.of cases	Perce-ntage	No.of cases	Perce-ntage	
Oedema	42	100.00	19	82.61	93.85
Oliguria	37	88.09	17	73.91	83.08
Diarrhoea	22	52.38	8	34.78	46.15
Nausea & vomiting	8	19.05	5	21.74	20.00
Fever	7	16.67	2	8.70	13.85
Headache	6	14.28	3	13.04	13.85
Altered sensorium	4	9.52	2	8.70	9.23
Gross hematuria	3	7.14	1	4.35	6.15
Convulsions	1	2.38	1	4.35	3.08

Profile of common presenting signs and symptoms is shown in table IV.

As it is evident from the table IV that oedema was present in 100% cases of group A and only 82.61% cases in group B and overall incidence of oedema was 93.85%. Oedema was soft and pitting. Oliguria was present in 88.09% of patients presenting for first time and 73.91% in patients of relapse, and overall in 83.08% cases. Gross hematuria was associated with 7.14% patients with initial episode and 4.35% with relapse and overall with 6.15%. Likewise nausea, vomiting was present in 19.05% and 21.74%

with initial episode and relapse respectively and overall it was in 20% patients. Diarrhoea was fairly common (52.38%) in group A and 34.78% in group B and overall in 46.15% cases. Altered sensorium was observed in 9.52% and 8.70% cases of group A and B respectively and overall in 9.23% cases. Fever at onset was present in 16.67% and 8.70% cases of initial episode and relapse respectively and overall in 13.85% cases. Headache was present in 14.28% cases presenting for the first time and in 13.04% presenting for second time and overall in 13.85% cases. Convulsions were observed in 2.38% cases of initial episode and 4.35% cases of relapse and overall in 3.08% cases.

TABLE V : Relevant past history.

History	Group A(N=42) Initial episode		Group B(N=23) Relapse		Overall Percentage (N=65)
	No.of cases	Percentage	No.of cases	Percentage	
U.R.I.	6	14.29	9	39.13	23.08
Cutaneous infections	3	7.14	3	13.04	9.23
Allergic episode	2	4.76	4	17.39	9.23
Malaria, jaundice/ or other relevant disorders.	1	2.38	-	-	1.54

Table V depicts that in no case history of jaundice, drug intake, related multisystem disorders could be elicited. Only one case (2.38%) had history of malaria in group A and overall in 1.54% cases. History of cutaneous

infection was present in 7.14% cases of group A and 13.04% of group B patients and overall incidence was 9.23%. History of URI was ellicitable in 14.29% in group A and 39.13% in group B patients and 23.08% of whole study group. 4.76% cases of group A and 17.39% of group B and overall in 9.23% cases had history of allergic episode like rhinitis.

TABLE VI : Profile of common signs at onset.

Signs	Initial episode (N = 42)		Relapse (N = 23)		Overall percentage (N=65)
	No.of cases	Percentage	No.of cases	Percentage	
Peri-orbital oedema & facial puffiness	42	100.00	19	82.60	93.85
Pedal oedema	34	80.95	14	60.87	73.85
Anterior abdominal wall	30	71.42	12	52.17	64.62
Ascites	23	54.76	10	43.48	50.77
Pleural effusion	2	4.76	-	-	3.08

The profile of signs at onset is depicted in table VI. It is evident from table VI that peri-orbital oedema and facial puffiness were present in 100% of cases presenting for the first time while in only 82.60% cases in relapse and overall incidence was 93.85% cases. Pedal oedema was present in 80.95% in group A and 60.87% in group B and in 73.85% cases of study group. Anterior abdominal wall oedema was ellicitable in 71.42% cases in group A and 52.17% in group B and 64.62% cases of total

study group. Ascites and pleural effusion were present in 54.76% and 4.76% cases with initial relapse and 43.48% and 0.0% patients with relapse respectively.

As it is evident from table VII that hypertension was noted in 13 cases (20%) while hematuria was present in 14(21.58%) cases. U.T.I. was observed in 10(15.38%) cases. Azotemia was there in 12(18.46%) cases, while hepatomegaly was present in 43.08% cases, anemia of variable degree was present in 48(73.84%) cases. In none of the children evidence of any multisystem disorder could be found.

TABLE VII : Findings at onset (N=65).

Signs	No.of cases	Percentage
Anemia	48	73.84
Hepatomegaly	28	43.08
Hematuria	14	21.53
Hypertension	13	20.00
Azotemia	12	18.46
U.T.I.	10	15.38
Multisystem disorder	-	-

It is evident from table VIII that maximum, 21 cases (32.30%) fell in months of October-December followed by 19(29.23%) cases in July-September. Together comprising of 61.53%(Approximately two thirds of cases). In January-March, 14(21.53%) cases and in April-June, 11(16.92%) cases were observed. Thus there was definite preponderance in.. latter half of the year.

TABLE VIII : Seasonal incidence (N=65).

Season	No.of cases	Percentage	
January-March	14	21.53	
April-June	11	16.92	
July-September	19	29.23	61.53%
October-December	21	32.30	

From the table IX, it is evident that 12 cases (52.17%) of group B (relapse group) had suffered one previous episode whereas 7(30.43%) cases had suffered from two and 2(8.70%) cases each had three or more previous episodes.

TABLE IX : Number of previous episodes in relapse cases (N = 23).

No.of previous episodes	No.of cases	Percentage
1	12	52.17
2	7	30.43
3	2	8.70
7 3	2	8.70

Table X analyses the pattern of biochemical abnormalities in nephrotic syndrome. It was observed that blood urea levels were raised in 12(18.46%) cases(overall), while they were raised in 9 (21.42%) cases in group A and 3(13.04%) cases in group B. Serum creatinine values were raised in 10(23.80%) and in 3(13.04%) cases in group A and

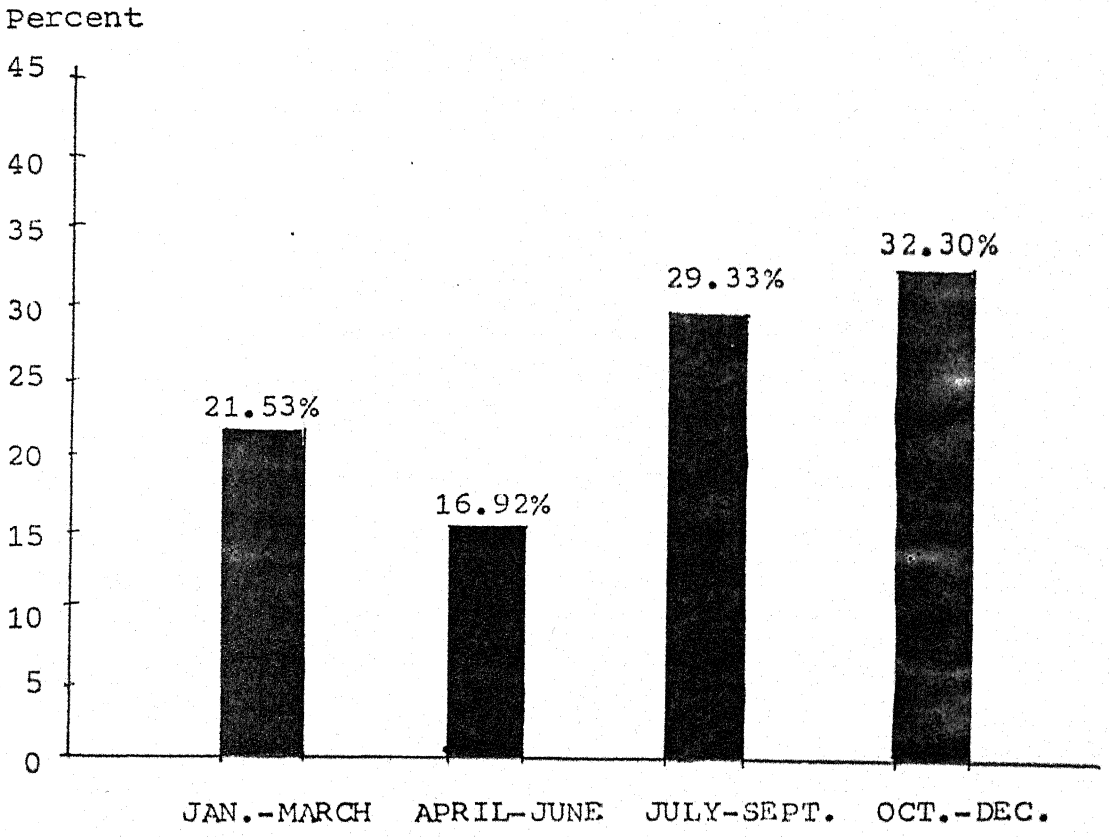


Fig. : SEASONAL INCIDENCE OF NEPHROTIC SYNDROME

B respectively and overall in 13(20%) cases. Serum cholesterol levels were raised in 54(83.08%) cases overall, in 39(92.86%) cases with initial episode and 15(65.22%) cases with relapse. Serum albumin levels ⟨2.5 g% were observed in 40 (95.24%) cases in group A and 15(65.22%) cases with relapse and overall 55(84.62%) cases.

TABLE X : Biochemical changes in nephrotic syndrome.

Indices	Group A (N=42) Initial episode		Group B (N=23) Relapse		Overall percentage (N=65)
	No.	Percentage	No.	Percentage	
Low serum albumin ⟨2.5 g%	40	95.24	15	65.22	84.62
Raised cholesterol ⟩200 mg%	39	92.86	15	65.22	83.08
Raised serum creatinine	10	23.80	3	13.04	20.00
Raised bloodurea ⟩40 mg%	9	21.42	3	13.04	18.46

Range of values for different indices in nephrotic syndrome was analysed and is shown in table XI.

As shown in table XI, 2+ urine albumin was observed in 2(3.08%) cases and 3+ urine albumin was in 3 (4.62%) cases. Majority of the cases, 60(92.31%) showed 4+ albuminuria. On analysing 24 hour urinary protein 19 (29.23%) cases had proteinuria between 50-100 mg/kg/day but majority of patients 28(43.08%) had proteinuria between

100-150 mg/kg/day while 14(21.54%) cases had more than 150 mg/kg/day proteinuria.

TABLE XI : Range of biochemical values observed in nephrotic syndrome (N=65).

Indices	Range of values	No.of cases	Percentage
Urine albumin	2+	2	3.08
	3+	3	4.62
	4+	60	92.31
24 hour urinary protein	50-100 mg/kg/day	19	29.23
	100-150 mg/kg/day	28	43.08
	7150 mg/kg/day	14	21.54
Blood urea	∠ 40 mg%	53	81.53
	40 - 100 mg%	10	15.38
	101-200 mg% or more	2	3.08
Serum creatinine	∠ 1.0 mg%	52	80.00
	1.0 - 1.5 mg%	9	13.85
	7 1.5 mg%	4	6.15
Serum cholesterol	150-200 mg%	11	16.92
	201-300 mg%	29	44.61
	301-400 mg%	19	29.23
	401-500 mg%	4	6.15
	7 500 mg%	2	3.08
Serum albumin	72.5 gm%	8	12.31
	1.5-2.5 gm%	43	66.15
	∠1.5 gm%	14	21.54

Fifty three (81.53%) cases had normal blood urea levels while 10(15.38%) cases had between 40-100 mg% blood urea and 2(3.08%) cases had more than 100 mg% blood urea levels. Likewise serum creatinine values were normal

in 52(80.0%) cases and between 1.0-1.5 mg% in 9(13.85%) caaes and more than 1.5 mg% in 4(6.15%) cases.

Serum chllesterol levels were within normal range in 11(16.92%) cases. Levels were slightly raised (200-300 mg%) in 29(44.61%) cases. 19(29.23%) cases were between 301-400 mg% and 4(6.15%) cases were between 401-500 mg% and only 2(3.08%) cases had serum cholesterol levels more than 500 mg%.

Normal serum albumin was observed in only 8(12.31%) cases while in range of 1.5-2.5 gm%, majority 43(66.15%) cases were studied and 14(21.54%) cases showed below 1.5 gm% serum albumin.

TABLE XII : Clinical category of patients.

Clinical category	No.of cases	Percentage
Having clinical presentation of MCNS	40	61.54
Not having presentation of MCNS	25	38.46

The uncomplicated child with nephrotic syndrome who was over the age of 1 year but under the age of 7 years and not having gross hematuria and hypertension and azotemia was assumed to be suffering from minimal change nephrotic syndrome (MCNS) and was not subjected to renal biopsy. As depicted in table XII, 40(61.54%) children represented this group while 25(38.46%) cases were having complicated nephrotic syndrome with features like gross hematuria, hypertension, or azotemia. Patients with poor

steroid response was likely to be having disease other than MCNS and were carefully selected for percutaneous renal biopsy for accurate diagnosis and to study clinico-pathologic correlation which is depicted in table XIII.

Out of 25 biopsied cases which were suspected to be having lesion other than MCNS 12(48%) still turned out to be MCNS. Bringing to total number of cases of MCNS to 52(80%). 4(6.15%) cases turned out be of focal glomerulosclerosis (FSGS) and membranoproliferative (MPGN) type each and 3(4.61%) cases of mesengial proliferative (Mes.PGN) group and 2(3.08%) cases of membranous nephropathy. In minimal change nephrotic syndrome group patients mean age was 5.49 years $\pm$2.65 S.D., hematuria(Microscopic) was present in 6(11.54%) cases while hypertension was present in 7(13.46%) cases. Azotenia was present in 4(7.69%) cases. Gross hematuria was not present in any of the cases and only 3(5.77%) cases required antihypertensives for treatment.

In focal glomerulosclerosis group mean age was 6.0 years. Hematuria and azotemia were present in 2(50%) cases each and hypertension was present in 1(25%) case. In membranoproliferative group hematuria was present in all 4(100%) cases and in 2 of them it was gross. Hypertension was present in 3(75%) cases and 2(50%) patients had azotemia. Mean age was 9.25 years.

One patient each (33.33%) had hematuria, hypertension and azotemia in mesengial proliferative group mwan age 6.35 years and one patient each (50%) was having hematuria, hypertension and azotemia in membranous nephropathy group, mean age 7.5 years.

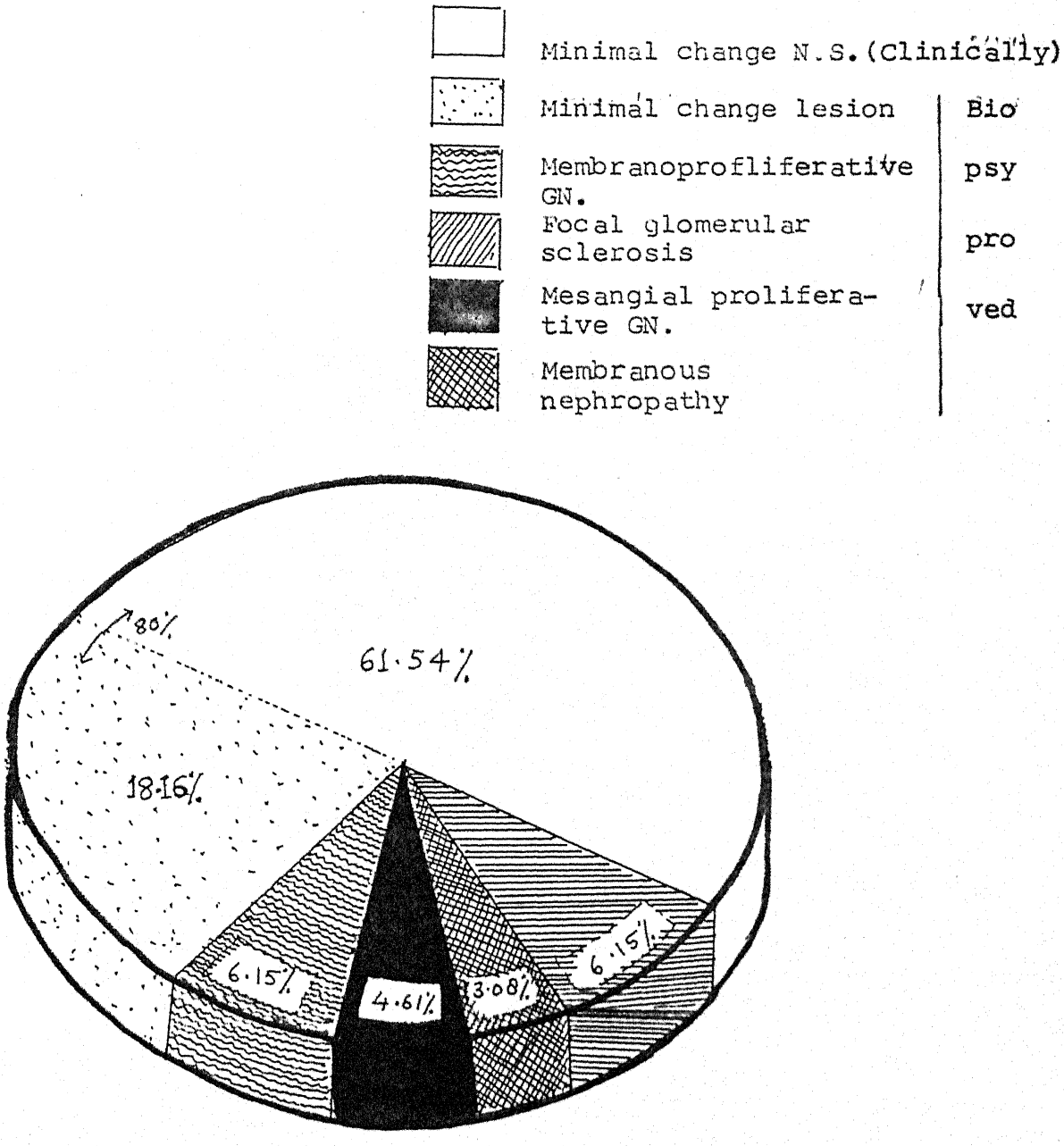


Fig. : UNDERLYING HISTOPATHOLOGY IN PRIMARY NEPHROTIC SYNDROME.

NATURE OF LESION

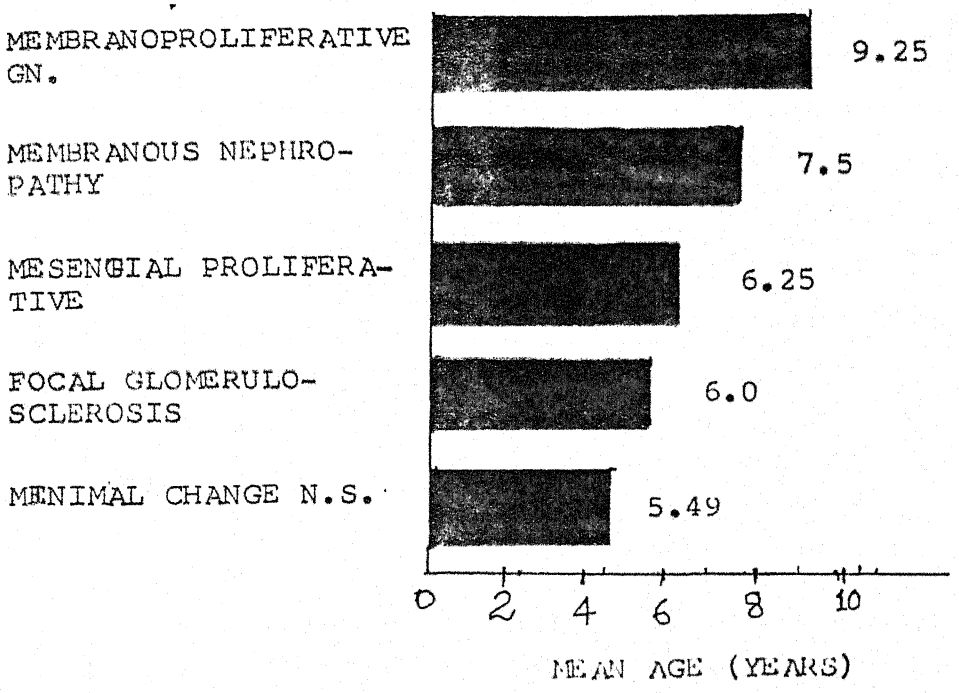


Fig. : MEAN AGE IN DIFFERENT HISTOPATHOLOGIC LESIONS OF NEPHROTIC SYNDROME.

TABLE XIII : Different lesions in nephrotic syndrome and clinical correlation (N=65).

Lesions	No. (%) of cases	Mean age (years)	Hematuria No. (%)	Hypertension No. (%)	Azotemia No. (%)
Minimal change nephrotic syndrome	52 (80%) (40+12)	5.49±2.65 SD	6 (11.54)	7 (13.46)	4 (7.69)
Focal segmental glomerulosclerosis	4 (6.15)	6.0	2 (50.0)	1 (25.0)	2 (50.0)
Membranoproliferative glomerulonephritis	4 (6.15)	9.25	4 (100.0)	3 (75.0)	2 (50.0)
Mesengial proliferative glomerulonephritis	3 (4.61)	6.35	1 (33.33)	1 (33.33)	1 (33.33)
Membranous glomerulonephritis	3 (3.08)	7.50	1 (50.0)	1 (50.0)	1 (50.0)
TOTAL	65	5.8	14 (21.54)	13 (20.0)	10 (15.38)

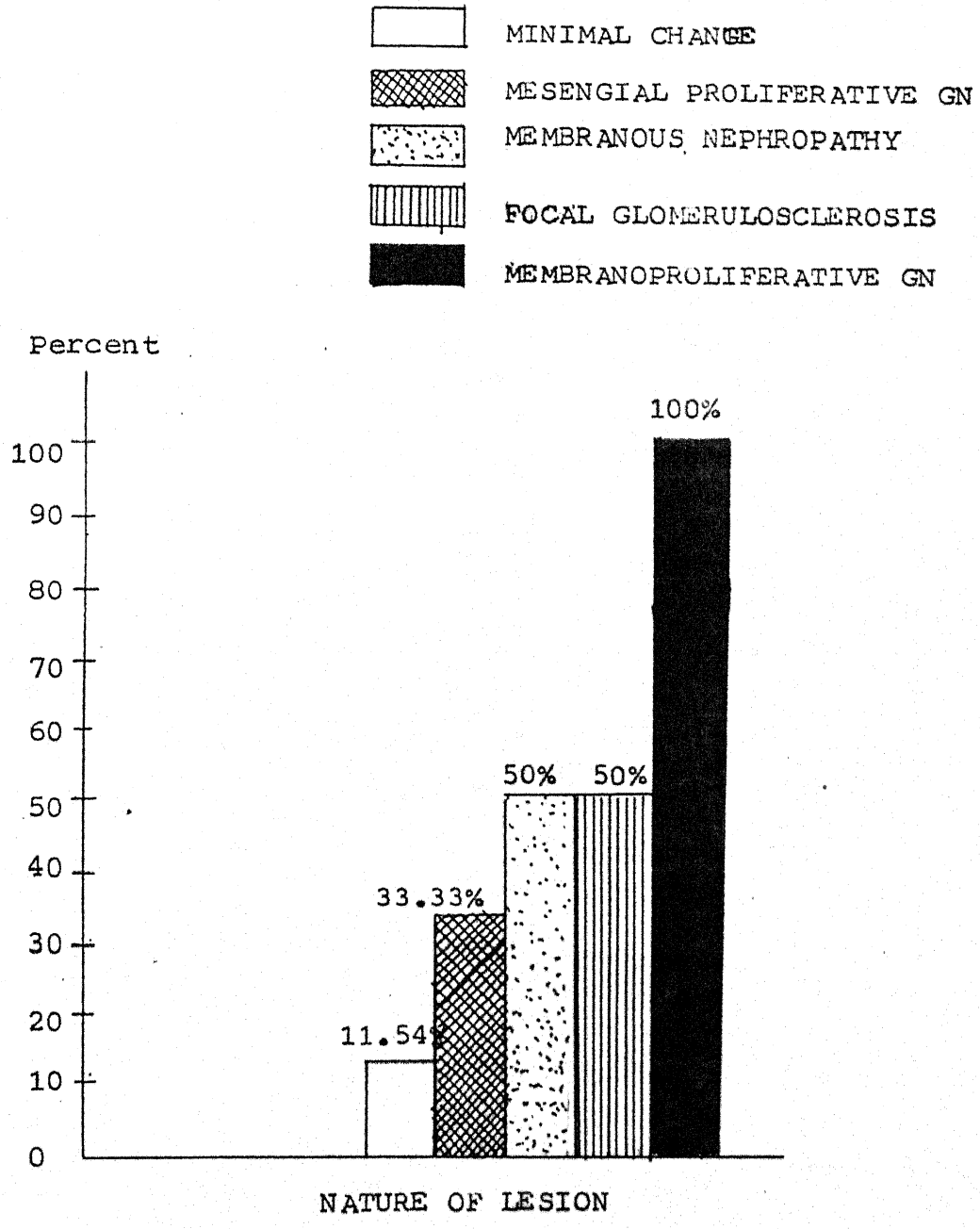


Fig. : INCIDENCE OF HEMATURIA IN NEPHROTIC SYNDROME

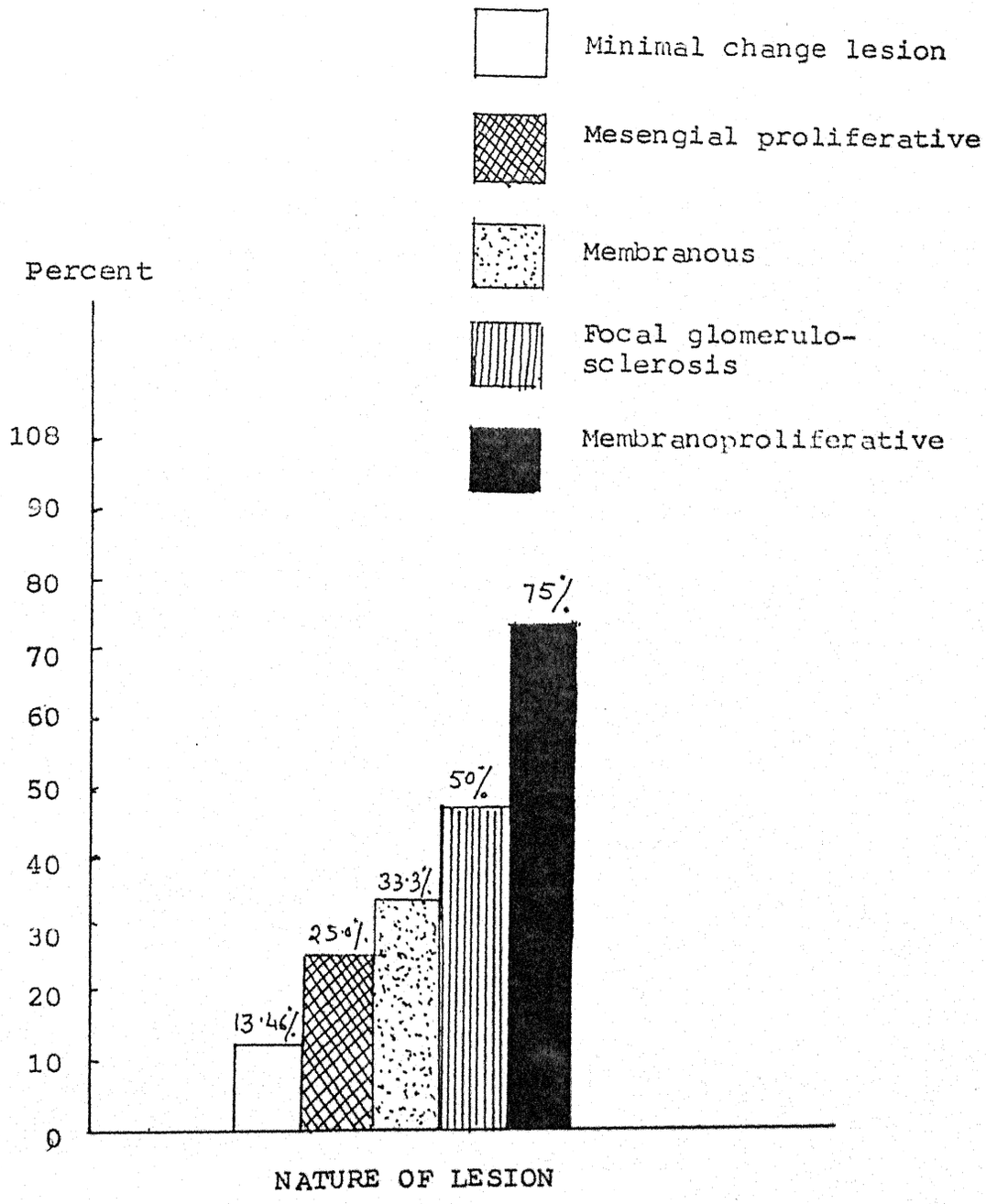
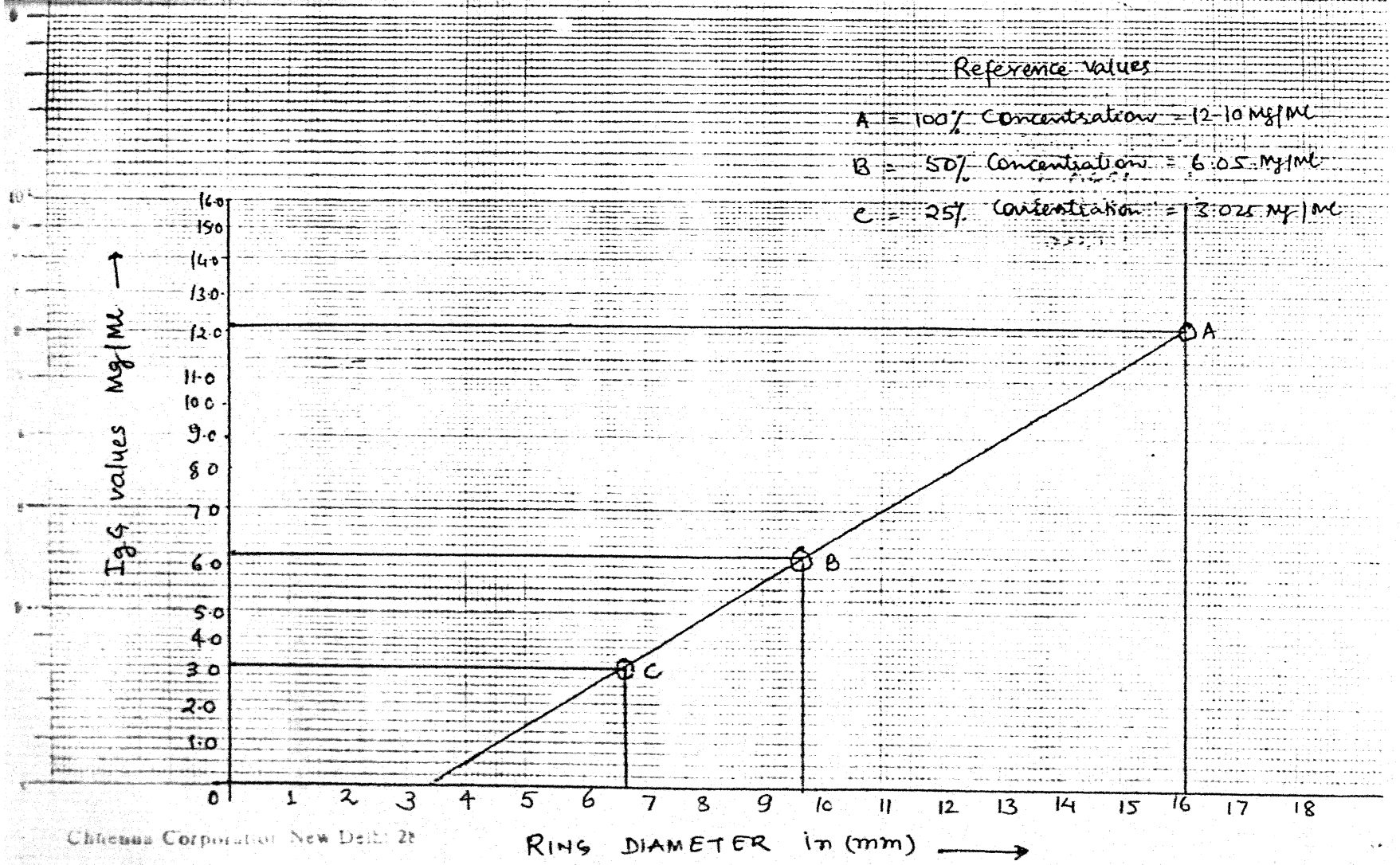
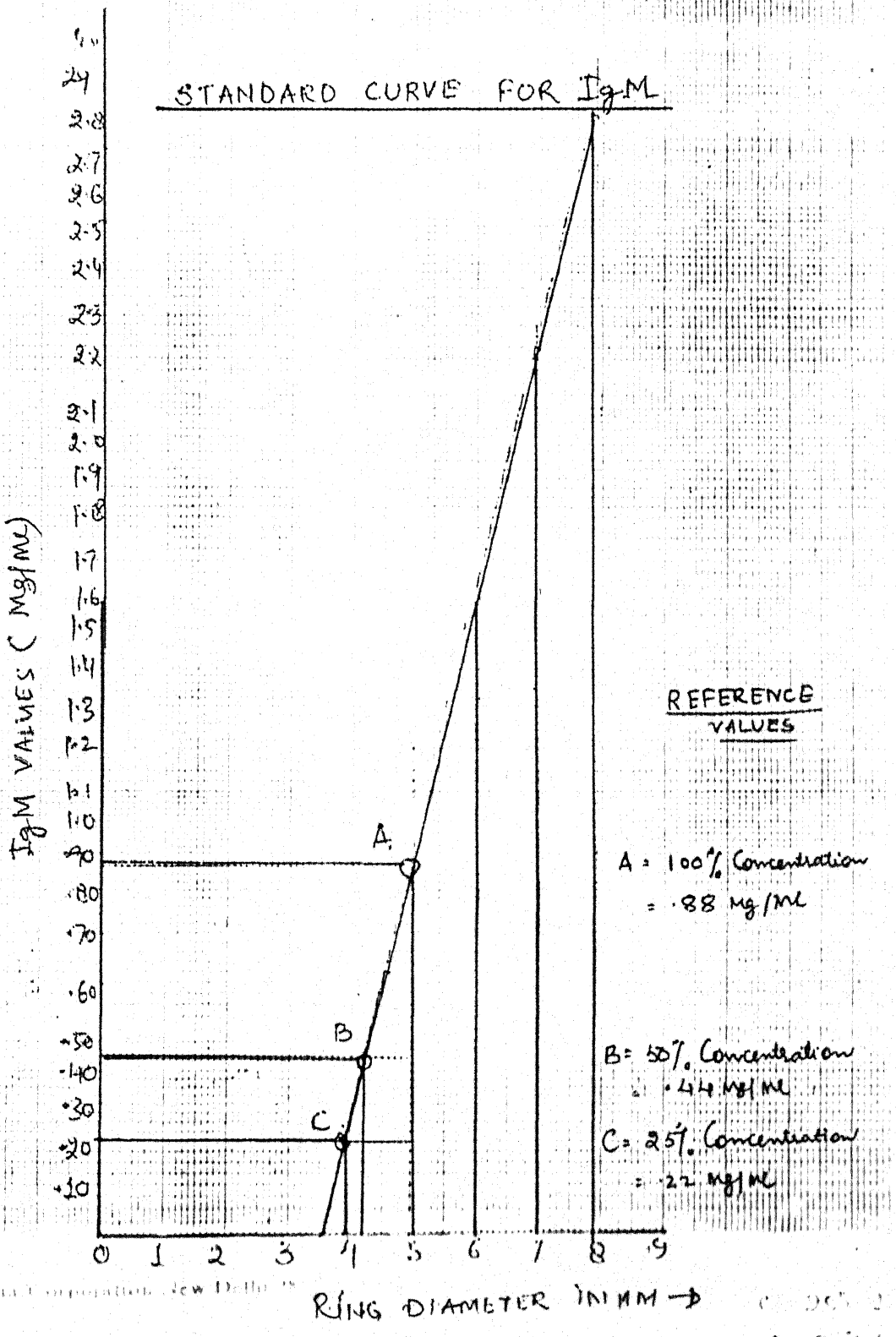
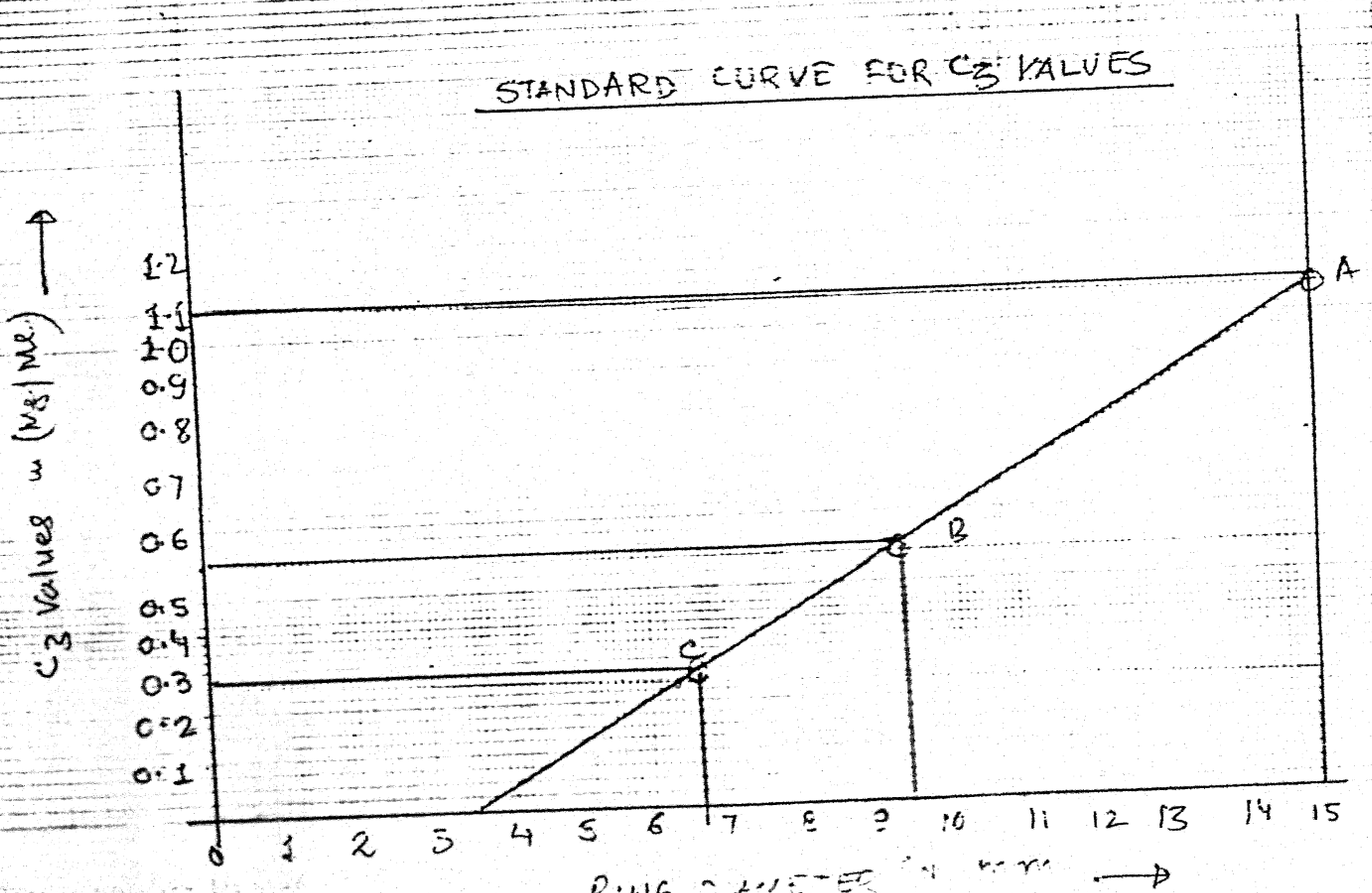


Fig. : INCIDENCE OF HYPERTENSION IN NEPHROTIC SYNDROME.

STANDARD CURVE FOR IgG LEVELS




STANDARD CURVE FOR IgM
IgM VALUES (Mg/ML)
2·8
2·7
2·6
2·5
2·4
2·3
2·2
2·1
2·0
1·9
1·8
1·7
1·6
1·5
1·4
1·3
1·2
1·1
1·0
·90
·80
·70
·60
·50
·40
·30
·20
·10
A
B
C
0 1 2 3 4 5 6 7 8 9
RING DIAMETER IN MM →
REFERENCE VALUES
A = 100% Concentration
= ·88 Mg/ML
B = 50% Concentration
= ·44 Mg/ML
C = 25% Concentration
= ·22 Mg/ML



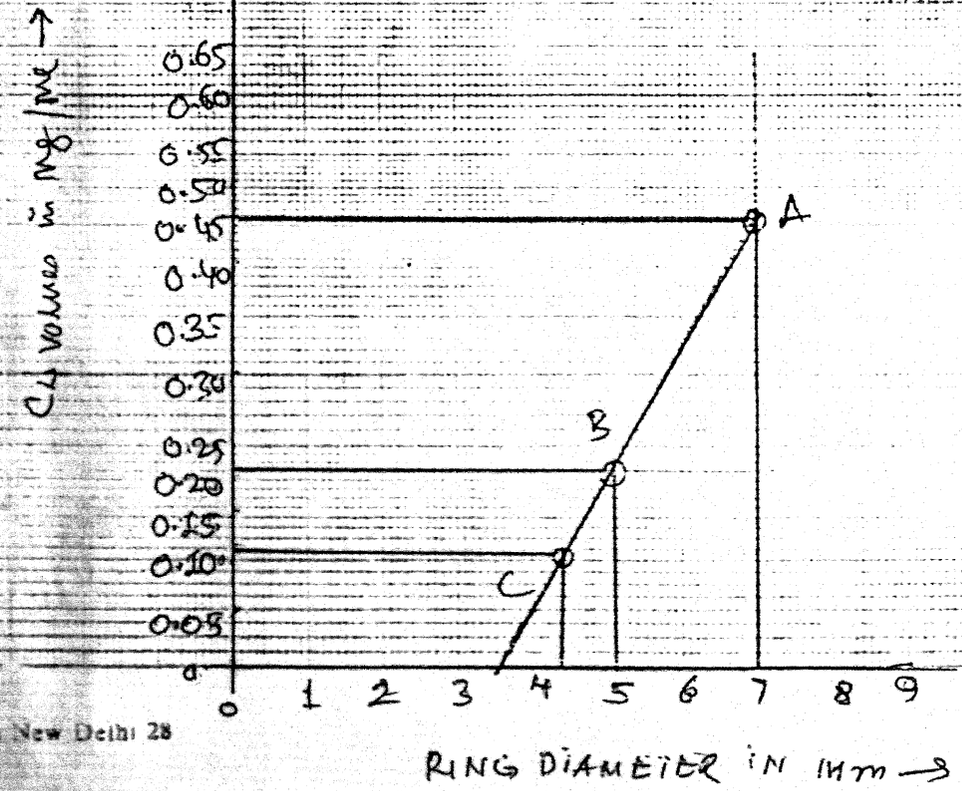
REFERENCE VALUES

A = 100% Concentration
1·1 Mg/ML

B = 50% Concentration
·55 Mg/ML

C = 25% Concentration
·275 Mg/ML

STANDARD CURVE FOR C_4 VALUES

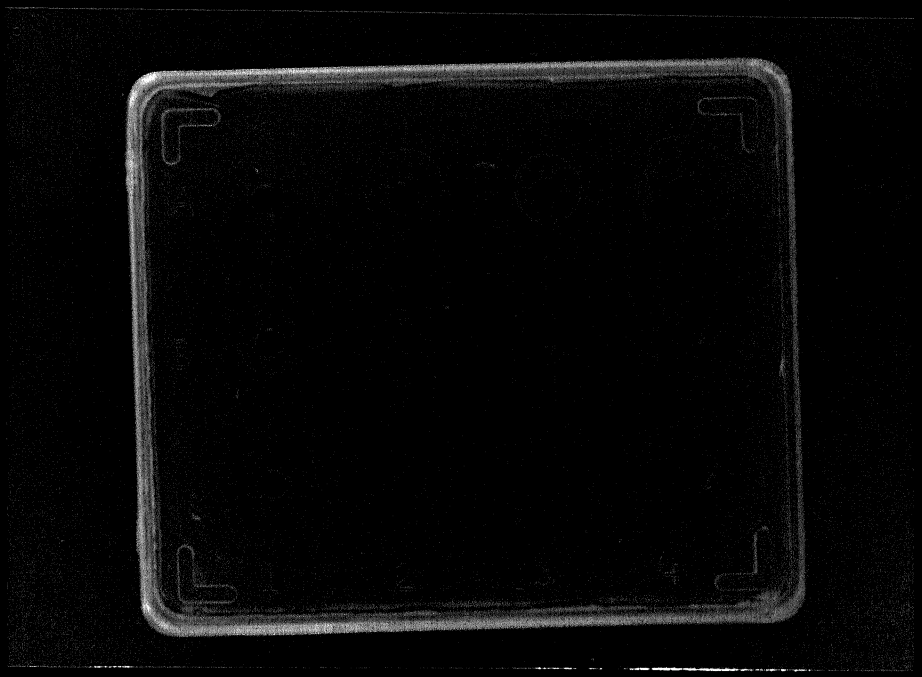


REFERENCE VALUES

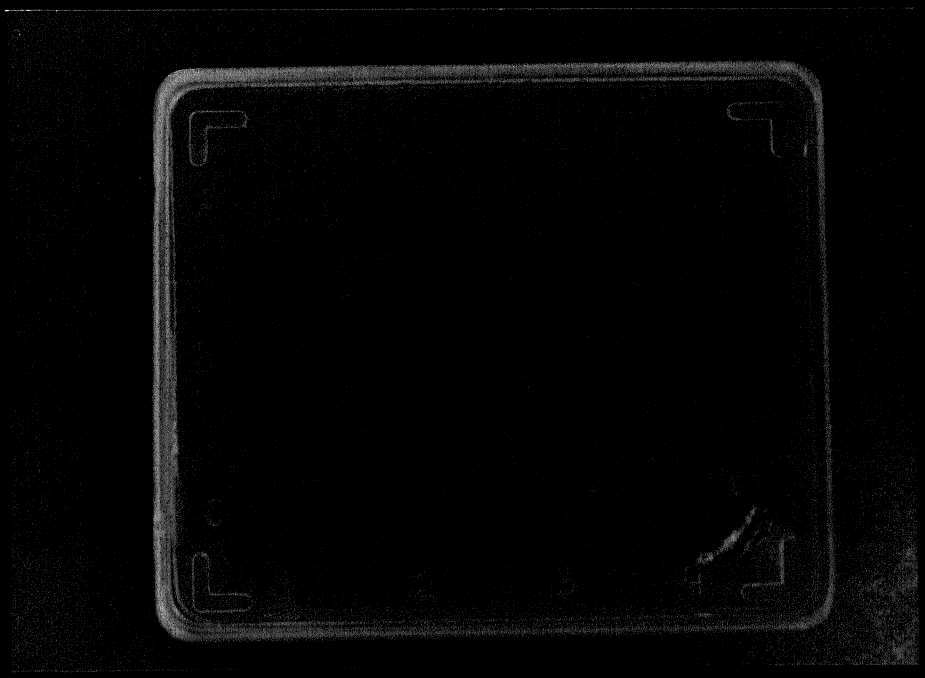
A = 100% Concentration : ·46 mg/ml

B = 50% Concentration : ·23 mg/ml

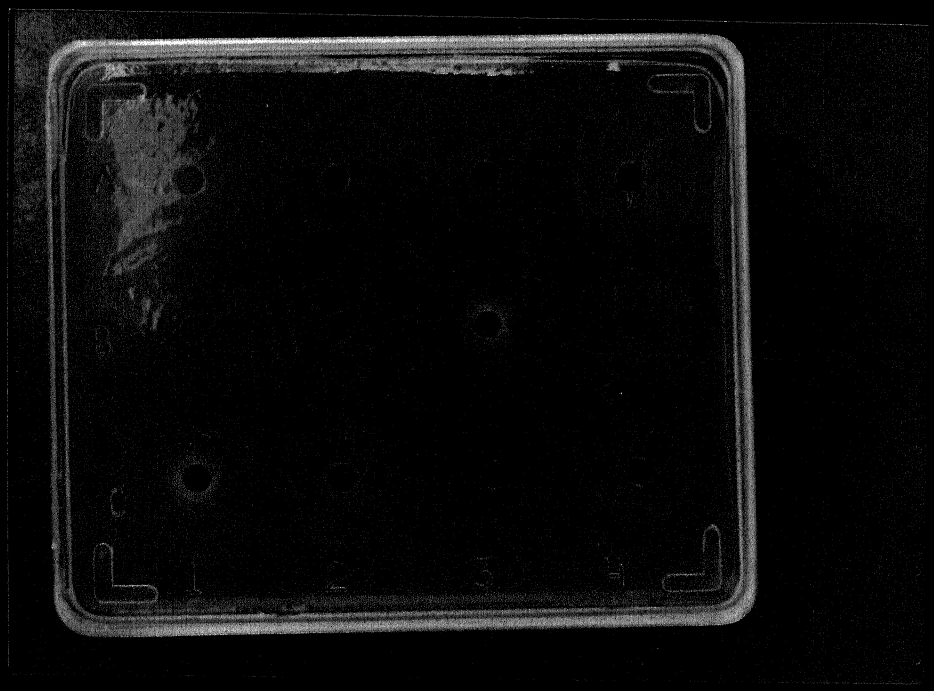
C = 25% Concentration : ·115 mg/ml



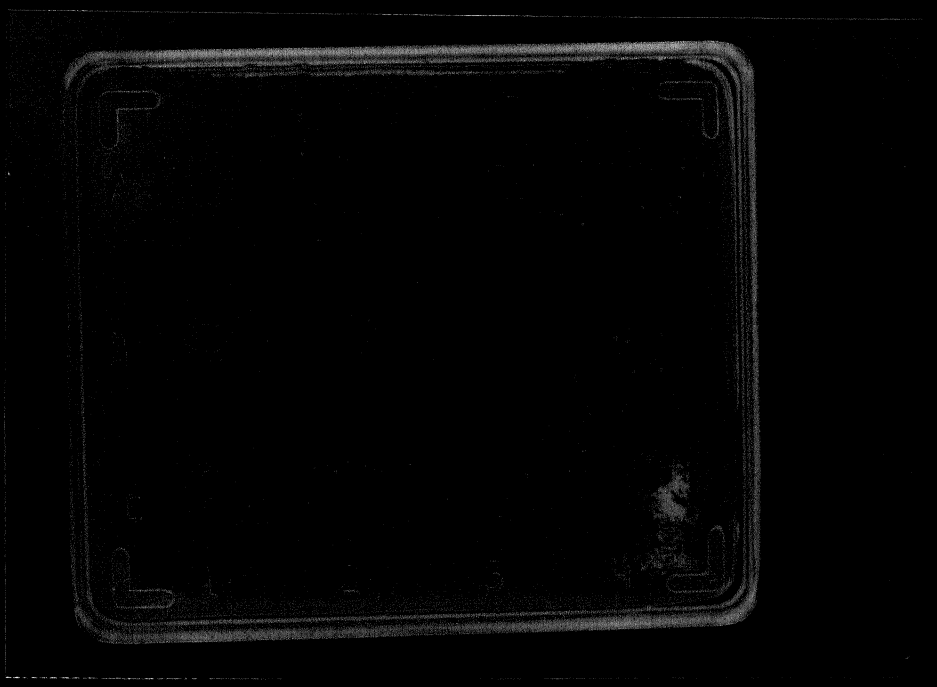
IgG IMMUNODIFUSION PLATE : Showing Immuno-precipitating Ring.



IgM IMMUNODIFUSION PLATE : Showing Immuno-precipitating Ring.



C_3 IMMUNODIFUSION PLACE : Showing Immuno-precipitating Ring.



C_4 IMMUNODIFUSION PLACE : Showing Immuno-precipitating Rings

Mean serum IgG levels in nephrotic group were 853.38±276.53 mg/dl which were low at statistically highly significant level ($p < 0.001$) as compared with control . On the contrary serum IgM levels were significantly raised ($p < 0.05$) i.e. 300.57±72.01 mg/dl as compared with 209.25±54.06 mg/dl in controls. Serum C_4 values were almost similar in both groups. Serum C_3 levels were low 107.71±35.39 mg/dl as compared with controls (130.25±15.99 mg/dl) but this was statistically insignificant ($p < 0.2$)

TABLE XIV : Immunological profile in nephrotic syndrome (Mean ± S.D., mg/dl).

Group	IgG	IgM	C_3	C_4
A. Control (N=24)	1777.50 ±124.73	209.25 ±54.06	130.25 ±15.99	38.39 ±6.22
B. Nephrotic syndrome (N=65)	853.38 ±276.53	300.57 ±72.01	107.75 ±35.39	39.22 ±8.11
p value	<0.001	<0.05	<0.2	

An attempt was made to correlate histopathological finding with immunological changes in table XV. From the table XV it can be seen that initial hypocomplementemia was present in 20% cases but it persisted only in 6.15% cases. Among the MCNS group only 7.7% children had hypocomplementemia but it persisted in none of them.

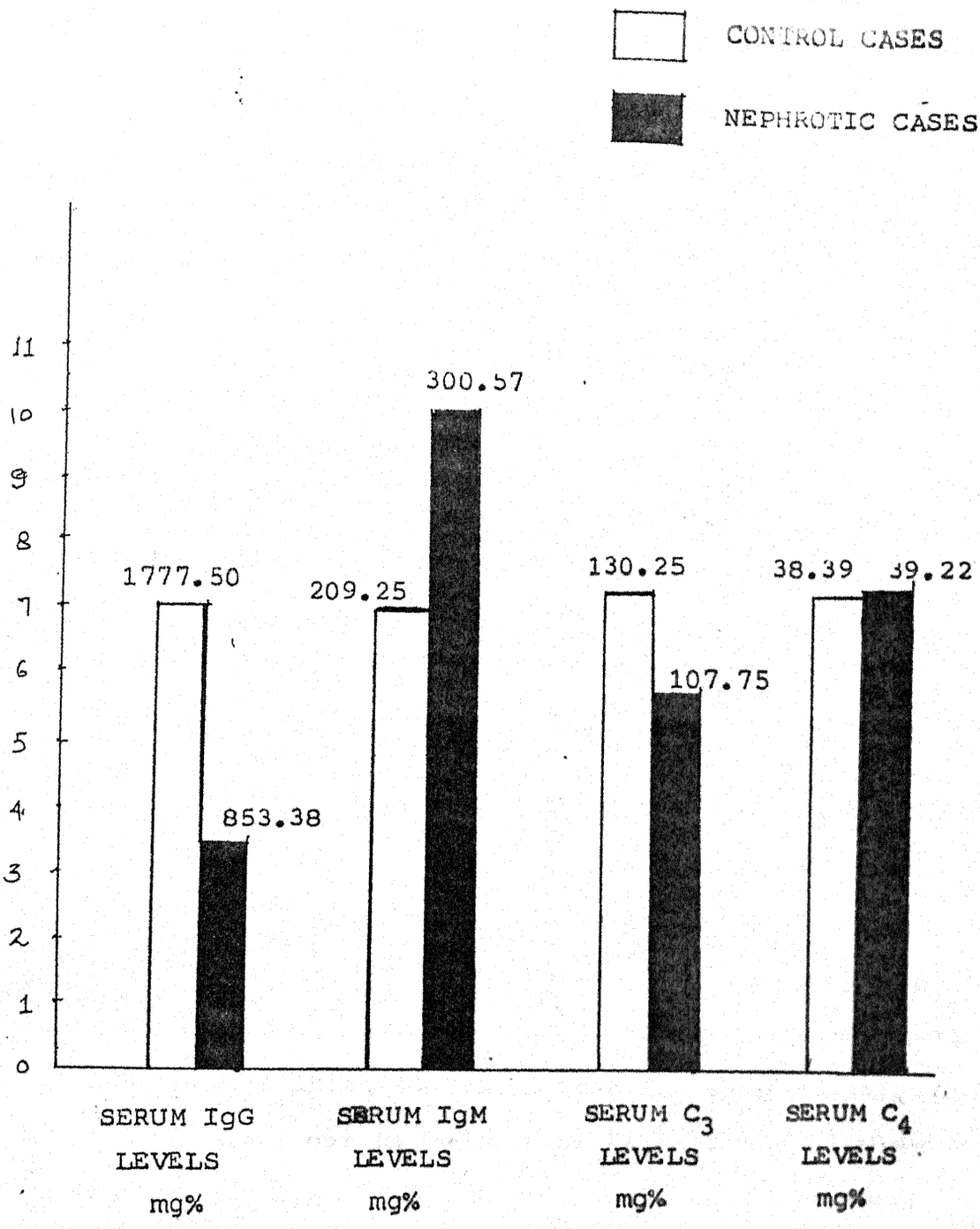


Fig. : SERUM IMMUNOGLOBULINS AND COMPLEMENT LEVELS IN NEPHROTIC SYNDROME.

Initially, hypocomplementemia was present in all the cases of membranoproliferative cases followed by 2 out of 3 in mesengial proliferative group. Persistence of low C_3 levels was seen mainly in membranoproliferative group.

TABLE XV : Pathological and immunological correlation.

Groups	No.of cases	Initial hypocompl-ementemia	Persistent hypocompl-ementemia
Minimal change N.S.	52	4(7.7%)	-
Focal glomerulosclerosis	4	1	-
Membranoproliferative glomerulonephritis	4	4	3
Membranous nephropathy	2	1	-
Mesengial proliferative	3	2	1
	65	13(20%)	4(6.15%)

Apart from symptoms and signs, response pattern to steroids was also analysed in relation of the case as shown in table XVI, as pattern of steroid response was a major decision making factor in selecting the patients for biopsy. Among non responder group of 6 patients which included both initial and late ones, all were biopsied and 2 of them turned out to be minimal lesion, one of them initial non responder and second, late non responder. Three cases were of membranous proliferative group and 1 showed membranous nephropathy. Among 13 frequently

TABLE XVI : Renal histology and response to steroids.

Response	No.of cases	No.of cases biopsied	Minimal change lesion	Focal glomerulo-sclerosis	Mesengial proliferative GN.	Membrano proliferative GN	Membranous glomerulo-nephritis
GROUP A							
Responders (other than pattern given below).	40	5	2	1	1	1	-
GROUP B							
Non responders(Initial + late)	6	6	2	-	-	3	1
GROUP C : Frequent relapsers	13	10	6	2	2	-	-
Group D: Steroid dependent.	6	4	2	1	-	-	1
TOTAL	65	25	12	4	3	4	2

relapsing patients, 10 were biopsied, 6 of them (60%) turned out to be minimal lesion, 2(20%) had focal glomerular sclerosis and 2(20%) cases were of mesengial proliferative group. In steroid dependent group of 6 patients, 4 were biopsied, 2 of them were minimal lesion, 1 was focal glomerulosclerosis and 1 membranous. There were 40 cases of more favourable steroid response. Out of these, 5 cases were biopsied due to indications like gross hematuria, hypertension or age on higher side, 2 of them were minimal lesion and 1 case each had focal mesengial proliferative and membranoproliferative lesion.

An attempt was also made to study the incidence of tuberculosis in nephrotic patients. As shown in table XVII, the incidence was estimated to be 18.46%.

TABLE XVII : Showing incidence of primary complex in nephrotic patients (N=65).

	No.of cases	Percentage
Tubercular	12	18.46
Not received steroid therapy	8	66.67
Already received steroid therapy	4	33.33

Out of 12 cases identified as tubercular 8(66.67%) cases had not received steroids earlier while only 4(33.33%) cases had received steroids already.

Regarding the management of nephrotic syndrome it was seen that though 13 cases with hypertension of variable degrees were detected, antihypertensives were required in 7(61.54%) cases only. In rest 5(38.46%) cases blood pressure returned to normal after salt restriction only and as oedema subsided. Diuretics were used only in 9(13.85%) cases in which child was distressfull due to oedema. In rest of the 56 cases (86.15%) oedema subsided on its own.

Antitubercular drugs were used in all 12 cases in which evidence of primary complex was present. Table XVIII depicts the pattern of use of steroids which were the mainstay of management and also of cyclophosphamide which was used in resistant, dependent cases, frequent relapsers and steroid toxicity.

TABLE XVIII : Drugs for induction and maintenance of remission.

Drugs used	For induction of remission (65)		For maintenance of remission (63)	
	Used No. (%)	Not used No. (%)	Used No. (%)	Not used No. (%)
Steroid	63(96.92)	2(3.08)	43(68.25)	20(31.75)
Cyclophos-phamide	8(12.31)	57(87.69)	1(12.50)	7(87.50)

As it can be seen from the table XVIII, steroids were used in 63(96.92%) cases for induction of remission and among them in 43(68.25%) cases for maintenamce of remission. In rest 20(31.75%) cases steroids

were not required for maintenance of remission. Cyclophosphamide was used in 12.31% cases and among them it was required for maintenance of remission in only 12.50% cases.

Table XIX shows the various types of response by steroid therapy. Two cases went into spontaneous remission. Steroids were used in 63 patients. It is clear that 61 (96.82%) cases were initial responders. It was seen that 6(9.52%) cases were steroid resistant. Out of them 2(3.17%) cases were early non responders and 4(6.35%) cases were late non responders. 6(9.52%) cases were steroid dependent Among the initial responders (61) most of the cases 46 (75.40%) responded to steroids within 2 weeks of initiation of therapy but 15(24.60%) cases were relatively slow responders, responding after 2 weeks of initiation of steroid 13(8.20%) cases were found to be frequent relapsers, 5 (8.20%) of them were steroid dependent and 8(13.11%) cases were not steroid dependent. 50(81.97%) cases were infrequent relapsers.

TABLE XIX : Response pattern to steroids (N=63).

Category		No.of cases	Percentage	
1. Initial responders		61	96.82	
2. Early non responders	Steroid	2	3.17	9.52
3. Late non responders	resistant	4	6.35	
4. Steroid dependent		6	9.52	
5. Relative slow responders		15	24.60	
6. Frequent relapsers with steroid dependent.		5	8.20	21.31
7. Frequent relapsers without steroid dependent.		8	13.11	
8. Infrequent relapsers		50	81.97	

Time taken to respond to therapy for different patients is analysed in table XX. It is quite evident that majority of the steroid responsive patients 46 responded within 2 weeks of initiation of steroid therapy (75.40%) i.e. 3/4th. Out of these 14(22.75%) responded within one week and 32(52.45%) cases within 2 weeks. Cases responding within 2-3 weeks were 7 (11.47%) and between 3-4 weeks were 5(8.20%). Only 2(3.28%) cases responded in 4-6 weeks and 1(1.64%) during 6-8 weeks interval.

TABLE XX : Time taken for response to steroids(N=61).

Response time (weeks)	No.of cases	Percentage	
0 -- 1	14	22.95	75.40
1 - 2	32	52.45	
2 - 3	7	11.47	
3 - 4	5	8.20	
4 - 6	2	3.28	
6 - 8	1	1.64	

In the table XXI an attempt has been made to depict the observations regarding relapse free interval on steroids administration. As it is evident maximum 24 (36.92%) patients had relapse free interval of 1-2 years followed by 14 (21.54%) cases having relapse free interval of 6-12 months. Twelve (18.46%) cases had relapse free interval of 4-6 months. Seven cases (10.77%) had relapse free interval between 2-4 months and 4 cases (6.15%) had

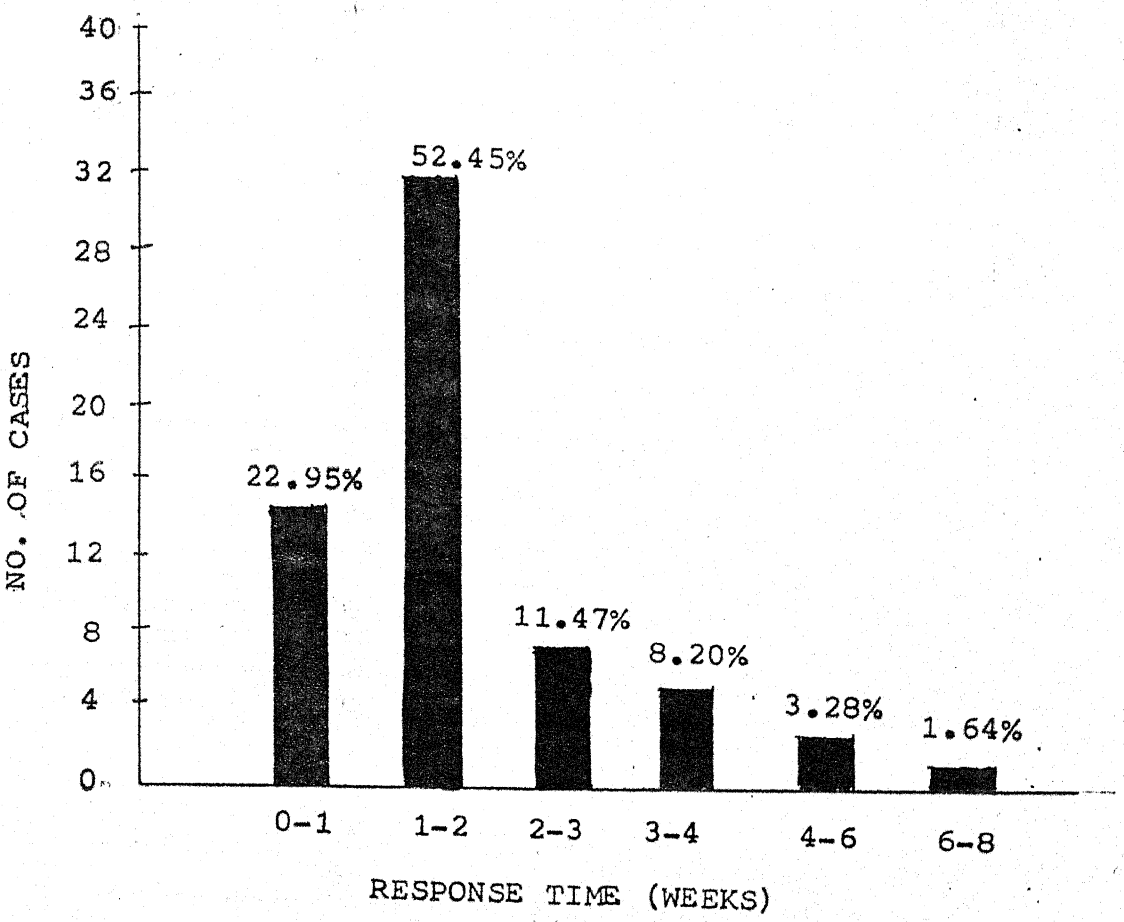


Fig. : TIME TAKEN FOR RESPONSE TO STEROIDS.

relapse free period of only 0-2 months. Similar number had relapse free interval of more than 2 years.

TABLE XXI : Relapse free interval on steroids administration (N=65).

Relapse free interval (months)	No.of cases	Percentage
≤ 2	4	6.15
2 - 4	7	10.77
4 - 6	12	18.46
6 - 12	14	21.54
12 - 24	24	36.92
≥24	4	6.15

TABLE XXII : Relapse free interval on cyclophosphamide (N=8).

Relapse free interval (months)	No.of cases	Percentage
0 - 6	2	25.00
6 - 12	2	25.00
≥ 12	4	50.00

Cyclophosphamide was the second line of drug in patients who either relapsed frequently or were steroid dependent, resistant or steroid toxicity was present. Table XXII shows that 4(50%) children remained in relapse for more than 1 year while 2(25%) remained in relapse for less than 6 months and 2(25%) remained in relapse between 6 to 12 months. None of our patients on cyclophosphamide

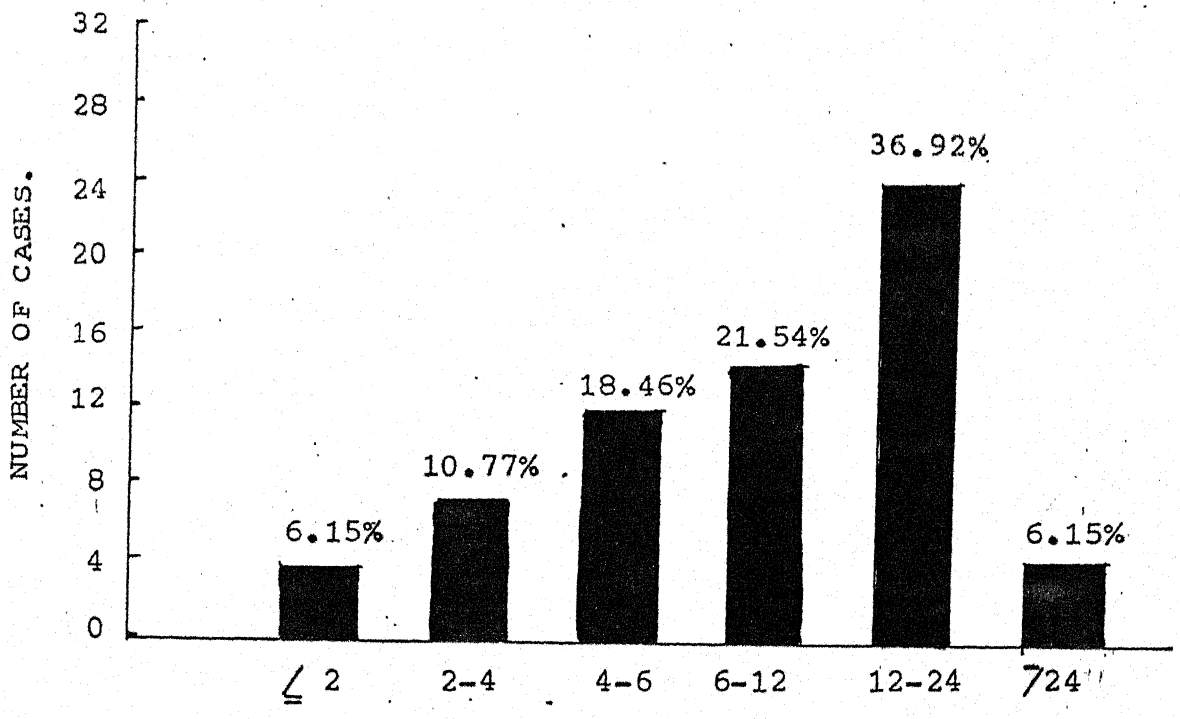


Fig. : RELAPSE FREE INTERVAL ON STEROIDS ADMINISTRATION.

had evidence of RBC in urine and none had significant leukopenia.

TABLE XXIII : Possible effect of tuberculosis on steroid response.

Response	No.(%) of cases (N=61)	With tuberculosis		Without Tuberculosis	
		No.	Percentage	No.	Percentage
Group A : Responding within 2 weeks of initiating steroid therapy.	46(75.41)	4	8.70	42	91.30
Group B : Responding later than 2 weeks	15(24.59)	5	33.33	10	66.67
Group C : Frequent relapsers	13(21.31)	3	23.08	10	76.92

An attempt was made to study various factors influencing response to steroids or contributing to the frequent relapsers. So that such patients may be identified earlier. Table XXIII depicts the effect of tuberculosis on response pattern. It was observed that out of 63 patients who were administered steroids, 61 responded initially. Among these 75.41% responded within 2 weeks of initiation of steroid therapy while 24.59% responded between 2-8 weeks. Among this group B 33.33% cases were tubercular as against the incidence of 18.46% of tuberculosis in present study group (Table XVII). Likewise in group C of frequent relapsers 3(23.08%) children had evidence of tuberculosis which is little more than 18.46%, the incidence of tuberculosis in present study group

(Table XXII). Among the patients responding within 2 weeks of induction of steroids only 4(8.70%) were tubercular. Mean response time in tubercular children was 25.3 days as against 16.7 days in non tubercular ones.

TABLE XXIV : Correlation of behaviour of patients in first 6 months and in any subsequent 6 months of disease (N=65).

No.of relapses in first 6 months	No.(%) of cases	No. of relapses in any subsequent 6 months			
		0	1	2	3
		No.(%)	No.(%)	No.(%)	No.(%)
0	29(44.61)	20(68.97)	6(20.69)	2(6.90)	1(3.45)
1	23(35.38)	14(60.87)	5(21.74)	2(8.70)	2(8.70)
2	9(13.84)	2(22.22)	2(22.22)	1(11.11)	4(44.44)
3	4(6.15)	-	-	2(50.00)	2(50.00)
TOTAL	65	36(53.38)	13(20.0)	7(10.77)	9(13.85)

Recognition of frequent relapsers poses a significant problem as a large group (21.31%) relapse frequently. Relationship of number of relapses in first 6 months and relapses in subsequent months was studied and is depicted in table XXIV. It was observed that 36(53.58%) cases did not suffer any relapse in subsequent 6 months. Thirteen (20%) cases suffered one relapse in subsequent 6 months period. Seven (10.77%) cases suffered two and 9(13.85%) cases suffered three or more relapses in subsequent 6 months period.

Among 29 cases (44.61%) who had not suffered any relapse in first 6 months period 20(68.97%) cases suffered none, 6(20.69%) cases suffered one, 2(6.90%) cases suffered

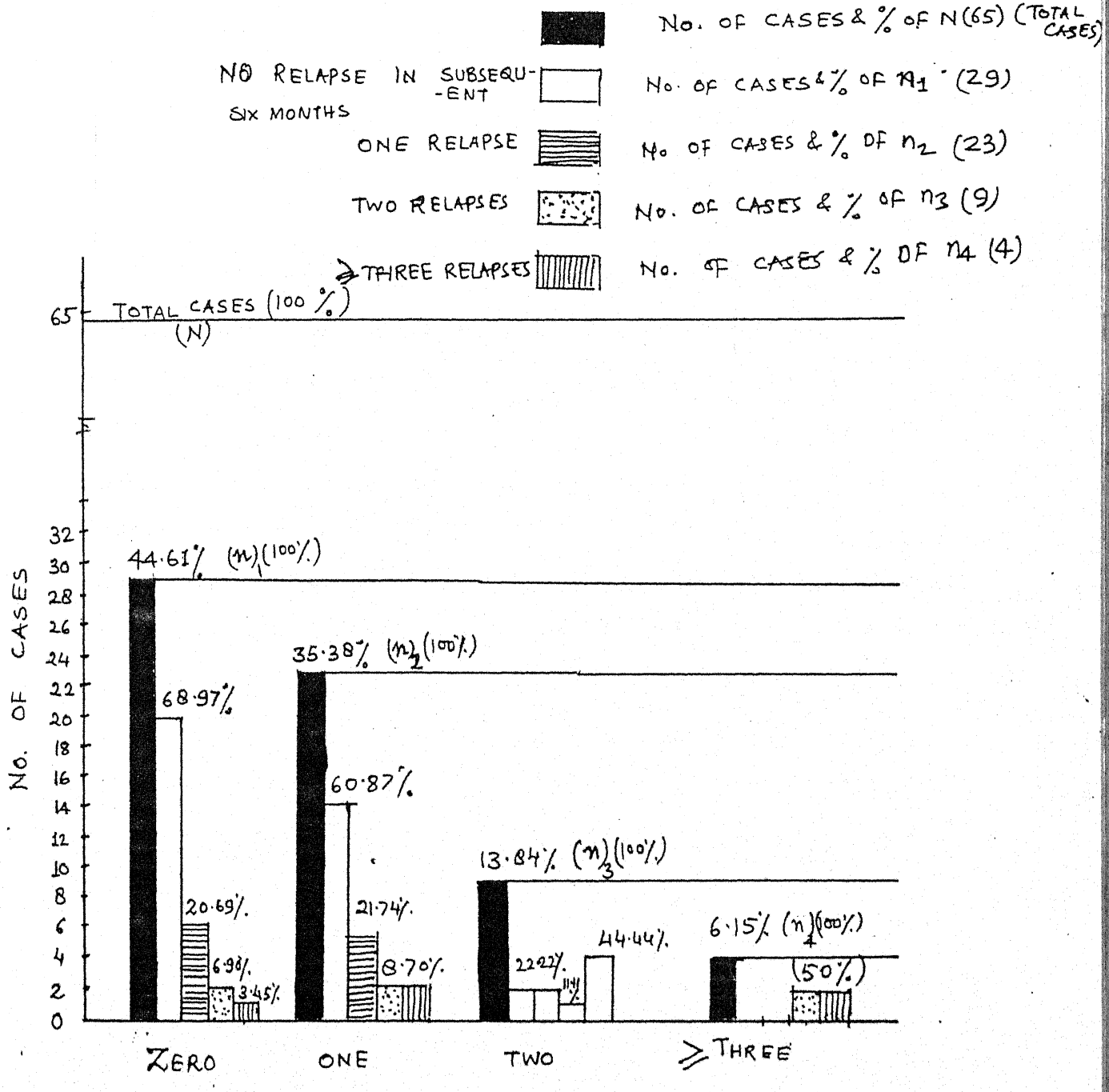


Fig. : CORRELATION OF RELAPSERS IN FIRST 6 MONTHS AND ANY SUBSEQUENT 6 MONTHS.

2 and 1 (3.45%) case suffered more than 3 relapses in subsequent 6 months. In contrast to this among 4 cases (6.15%) who had suffered more than or equal to 3 relapses, 2(50%) cases suffered more than 2 or 3 relapses in subsequent 6 months.

In the table XXV correlation of clinical features at onset and frequent relapsers and steroid resistant and dependent cases have been depicted. 10 (22.72%) patients of less than 6 years of age were frequent relapsers while 3(14.28%) cases were more than 6 years of age were frequent relapsers. Among hypertensives 3(23.08%), among hematuria group 4(28.57%), among azotemia group 2(20%) cases were frequent relapsers. The incidence of frequent relapsers in study group was 20%. Among resistant group of cases less than 6 years age patients had only 1(2.27%) cases, more than 6 years of age group had 5(23.81%) cases as resistant, while among hypertensives 3(23.08%), among hematuria 3(21.43%) and with azotemia patients 4(40%) cases had steroid resistance.

In steroid dependent group in less than 6 years of age 3(6.82%) cases were steroid dependent, among more than 6 years of age 3(14.29%) cases among hypertensives 1 (7.69%) and among hematuria cases 1(7.14%) and among azotemia 1(10%) case were steroid dependent cases.

TABLE XXV : Correlation between clinical features and steroid response. (N=65).

Clinical features	No. (%) of cases	Frequent relapsers No. (%)	Resistant No. (%)	Dependent No. (%)
Age <6 years	44(67.69)	10(22.72)	1(2.27)	3(6.82)
Age >6 years	21(32.31)	3(14.28)	5(23.81)	3(14.29)
Hypertension	13(20.00)	3(23.08)	3(23.08)	2(7.69)
Hematuria	14(21.54)	4 (28.57)	3(21.43)	1(7.14)
Azotemia	10(15.38)	2(10.00)	4(40.00)	1(10.00)

Cases were followed up to study the relapses (Table XXVI). History of U.R.I., allergic episodes or other infections was ellicited and it was observed that in 49% cases there was positive history of U.R.I. or allergic episodes. In 28% cases of relapse history or evidence of URI was present in 21% of allergic episodes, in 4% evidence of U.T.I. and in 7% evidence of cutaneous or other infection were present. In 40% cases no known factors was traceable.

TABLE XXVI : Relationship of relapses with URI and allergic episodes.

History or evidence	Percentage of relapse cases	
U.R.I.	28.00	49.00
Allergic episodes	21.00	
U.T.I.	4.00	
Cutaneous or other infections	7.00	
No known factor	40.00	

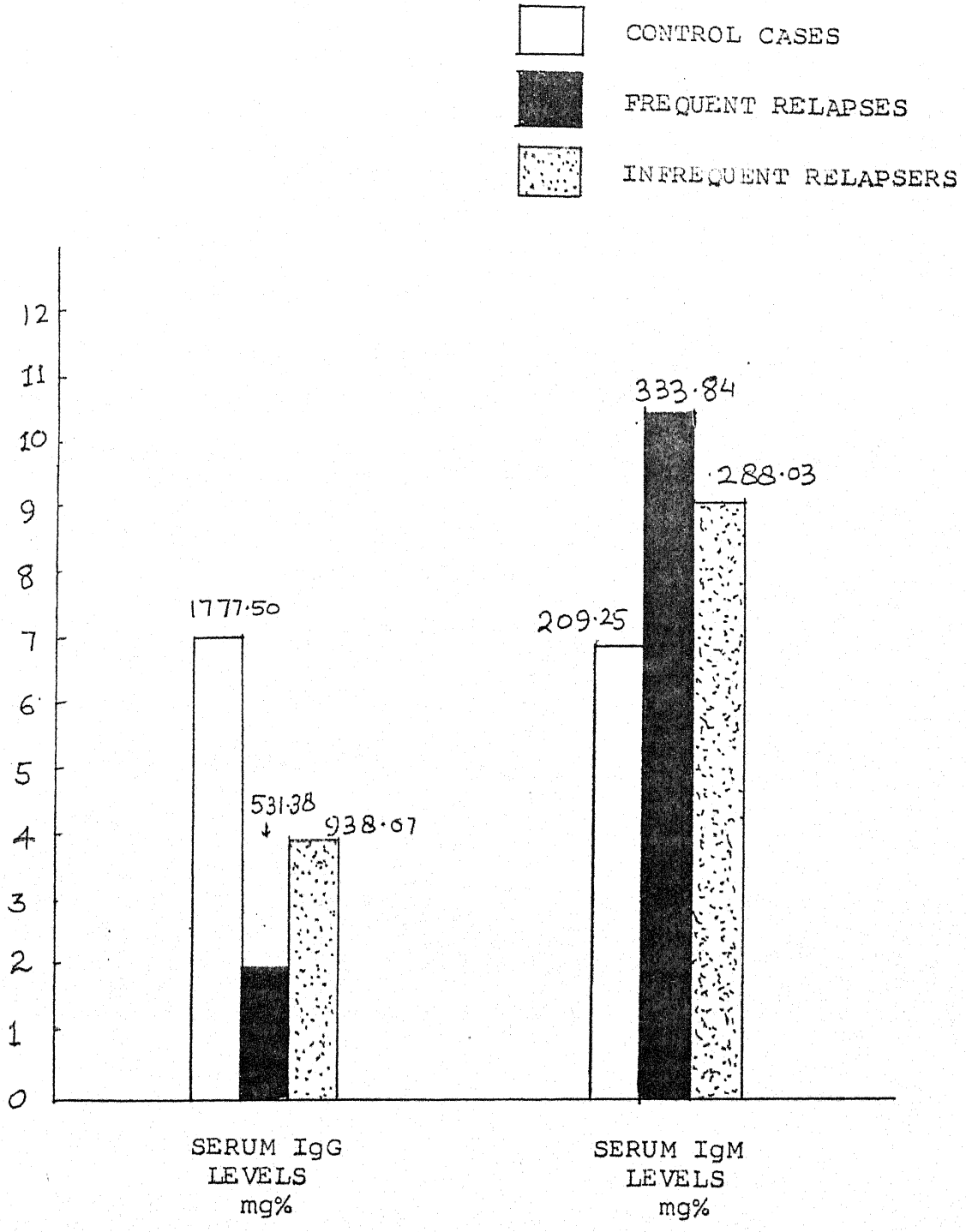


Fig. : VERY LOW SERUM IgG AND HIGH SERUM IgM LEVELS IN FREQUENT RELAPSERS.

It was one of our aims to identify markers for early recognition of frequent relapsers (Table XXVII). Apart from clinical basis immunological factors were searched for as in table. From this it is obvious that serum IgG levels were very significantly low in frequent relapsers (531.38±132.87 mg/dl) as compared to infrequent relapsers (938.07±250.30 mg/dl) ($p < 0.001$).

Serum IgM levels were concomittantly raised (333.84±79.42 mg/dl) in frequently relapsers versus infrequent relapsers (288.03±68.18 mg/dl) and this was found significant in statistical analysis ($p < 0.05$).

TABLE XXVII : Very low IgG levels in frequent relapsers. (Mean ± S.D., mg/dl).

	Groups		IgG	IgM
A	Control		1777.50±124.73	209.25±54.06
B	Frequent relapsers		531.38±132.87	333.84±79.42
C	Infrequent relapsers		938.07±250.30	288.03±68.18
	p	B : C	<0.001 Highly significant	<0.05 Significant

DISCUSSION

D I S C U S S I O N

The present study was carried out in the department of Pediatrics, M.L.B. Medical College, Hospital, Jhansi, over a period of two years from August, 1991 to July, 1993.

The study was aimed to evaluate the clinical, pathological and immunological changes associated with nephrotic syndrome in children of this region. It was our endeavour to study response pattern to steroid therapy. Besides, clinico-pathological correlation it was also our aim to identify the factors by which one can predict the response pattern of steroids, or identify frequent relapsers.

A total of 65 cases of nephrotic syndrome were examined in the present study. The incidence of nephrotic syndrome among total pediatric admissions was observed to be 1.62%.

As also observed by earlier workers, it was found to be the commonest nephrotic entity in children presenting with renal disease (72.2%).

In our study we observed a preponderance of male children. Male : female ratio was observed to be 1.8 : 1. Similarly higher incidence of male children in nephrotic syndrome has been reported by Mc Enery et al (1982) and Saxena et al (1988), viz 2:1, 2.5:1 and 3:1 respectively. Prasad et al (1985) reported M : F ratio to be 1 : 1.

Mc Enery (1982) however reported this ratio to be 1:1 in adolescence. Heymann et al (1972) reported male : female ratio to be 1 : 1.

Concordance that had been described in monozygotic but not in non zygotic twins, suggested existence of undefined genetic factors. Male preponderance suggest some degree of X linked linkage (Norio et al,1963).

The tendency towards small family size perhaps has caused non recognition of existence of X linked form of nephrosis. This entity may particularly account for male preponderance (Awadalla et al, 1989).

Many workers have reported increased incidence of nephrotic syndrome in sibs of affected child. Habib et al (1968) and (1973); Moncrieff et al (1973), Robin et al (1981) and Elzonski (1984) observed familial tendency to aquire nephrotic syndrome in 2-8%, 3-5%, 3.3%, 3.3% and 2.7% respectively. Michael et al (1974) reported incidence 1000 times greater, the incidence of nephrotic syndrome in sibs. But none of the sibs or members of the family of present study group were found to be suffering from nephrotic syndrome.

Further an attempt was made to categorise the various cases of nephrotic syndrome in different age groups. It is evident from table II that maximum incidence of nephrotic syndrome was observed between 4-6 years of age and nearly two third (64.61%) of the cases were between

1-6 years of age group. Brenner (1982) and Barakat(1986) reported that 60% patients of idiopathic nephrotic syndrome belonged to age group 2-6 years. Mc Enery(1982) reported 74% incidence of MCNS between 2-7 years while Saxena et al (1987) observed that majority of patients of MCNS were of ⩽6 years age (mean age 5.8 years). Mean age of onset observed in this study was also same (5.8± 2.65 SD years), Saxena et al (1988) had observed mean age 7.5 years in their study.

Vaishnav and Chaudhary (1983) reported 31.6% cases having age of onset between 1-3 years while in this study 23.08% cases were observed in same age group. They observed 30.8% cases between 4-6 years age group while in study 41.53% cases fell in this group of age which is a little higher. But over all Vaishnav et al (1983) observed 62.4% cases between 1-6 years of age which is almost similar to observations of present study (64.61%).

Not all patients who came into contact for the first time were having onset of their illness from then only. 42 cases (64.61%) were having first episode of illness (Group A) and 23 cases (35.39 %) were in different stages of relapse (Group B - Table III).

Though many workers have commented upon clinical presentation of nephrotic syndrome, none of them have studied or compared the clinical presentation of patients with initial episode (Group A) and patients with relapse (Group B). As it is known that many times in relapse

stage classical clinical picture of anasarca may not be there, we felt appropriate to study presentation of group B separately.

As presence of oedema is included in definition of nephrotic syndrome by International study of Kidney diseases in children and other workers its presence in all 42 cases (100%) with initial episode was natural but it was present in only 19 cases (82.61%) out of 23 cases of relapse (Group B).

As Rance et al (1976) defined relapse as oedema or 2+ reaction of urinary albumin ror 7 consecutive days, it is clear that presence of oedema is not necessary for labelling it as a relapse. Trainin et al (1975) defined relapse as proteinuria 2+ for 3 consecutive days. But some some workers have thought presence of oedema necessary for relapse. In our opinion patient can be in relapse even without evidence of edema. Though there is generalised oedema, in most of the nephrotic cases, it is the peri-orbital oedema which is commonest. As evident from table VI, it was present in all the cases (100%) of group A while in 82.60% cases of group B. Pedal oedema was present in 80.95% cases of initial episode and 60.87% of relapse cases. Anterior abdominal wall oedema was also ellicitable in less cases of group B (52.17%) cases as compared to 71.42% cases of group A.

The second commonest presentation was complaint of passing less urine (oliguria) 37 cases (88.09%) of

group A had oliguria while its incidence was comparatively lower (73.31%) in group B cases (Table IV). Cause of oliguria is due to hypovolumia which is in turn due to decreased plasma oncotic pressure due to loss of albumin.

Diarrhoea or abdominal symptoms were third common complaint in this study group being present in 52.38% group A and 34.78% group B cases. Though its association with nephrotic syndrome is commonly reported, it has not been expressed in terms of percentage by now. Cause of diarrhoea could be usually intestinal wall oedema which is the part of generalised oedema. This may give rise to complaint of pain in abdomen also, in these patients. As incidence of oedema is less in group B patients. Incidence of diarrhoea was also expected to be less.

Fever was associated in 16.67% of group A and 8.70% cases of group B. Its presence can be explained by concomittant infection like UTI or ARI due to lower immunity levels.

Altered sensorium is form of drowsiness or apathy was evident in 9.52% cases of group A and 8.70% cases of group B, due to raised blood urea levels. One patient in each group (overall 3.08%) had convulsions due to hypertension.

Gross hematuria was evident in 7.14% cases of group A and 4.35% cases of group B, so chances of having hematuria was less in relapse. Gross hematuria was

uncommon in Minimal Change Nephrotic Syndrome (1.1%) as reported by Mc Enery et al (1983), while it was present in 20% cases of membranous nephropathy.

Table V depicts the relevant past history in both group A and B of present study. Special emphasis was given to elicit history for identification of secondary causes like drugs (captopril, probencid, renographic medium), infections like malaria, syphilis, hepatitis and any cardiovascular cause or familial multi-system disorders but in none of present study group history of any of above factor could be elicited except for one case in which history of malarial pyrexia was there just preceding to onset of nephrotic syndrome (overall, 1.54%). While earlier workers have demonstrated secondary causes in 5-10%.

Nevertheless history of URI was present in 14.29% cases of group A and 39.13% cases of group B. Evidence of allergic episode like asthmatic bronchitis was there in 4.76% patients of group A and 17.39% cases of group B. In none of our cases there was preceding evidence of urticaria or bee sting.

Association of nephrotic syndrome have been reported with seasonal allergies by Cameroon et al (1975) and atopic disease by Thomson et al (1974) but they have not indicated the percentage in their study.

Meadow et al (1981) searched for such provocative factors and observed that onset of syndrome or relapse

was often linked with a cold or a runny nose by the parents. In few cases it was clearly a viral infection affecting others in family. If such cases had been included as examples of allergic rhinitis (which they may be), the incidence of atopy in nephrotic children would have gone very high. This was quite high 49% in relapse cases and 25% in initial episodes in study conducted by Meadow et al (1981).

Evidence of cutaneous infection was present in 9.23% cases of all groups,of this study significance of which could not be ascertained as they have not been thought to be a provocating factors by the previous workers.

Fluid ultimately collects in pleural and peritoneal cavities. Ascites was ellicitable in 54.76% cases and pleural effusion in 4.76% cases of group A and 43.48% and 0% cases of group B (Table VI).

Fluid collection was less in all instances in group B as oedema is also in lesser cases in this group.

Above figures could not be compared in absence of literature.

Due emphasis could be given to note anemia which was present in 73.84% cases (even with haemoconcentration presumed to be due to associated hypovolemia), and hepatomegaly in 43.07% cases. High percentage of anemia may be due to poor nutritional status of children in this backward region.

Hematuria was present in 21.53% of cases (Table VII). Habib et al (1971) reported it to be present in 13 to 29% cases, while White (1971) reported it in 13% cases. These observations are nearly same as present study, but Saxena et al (1988) had reported hematuria in 48% cases of nephrotic syndrome which is quite high as compared to the findings of present study.

Hypertension was reported to be present in 9% by White (1971), ISKDC reported it to be in 6 to 13% cases and that too mild and transient. Rance et al (1976) reported it in 9% in uncomplicated nephrotic syndrome. Saxena et al (1988) reported it to be present in 50% of cases which was quite higher as compared to present study (20%). Sonjakuster (1990) reported hypertension in 19% cases almost like the findings of present study (20%) but according to Bohlin et al (1984) it is not present in any case of MCNS.

Azotemia was observed in 18.46% of cases in present study. Saxena et al (1988) reported it in 28% cases which is relatively higher.

Mc Enery et al (1982) observed raised blood urea and serum creatinine levels in nearly 29% children with MCNS. This alteration in glomerular filtration is thought to be secondary to hypovolumia and restores following diuresis and resolution of proteinuria in those patients.

UTI was traceable in 15.38% cases of present study, which might be the cause of fever in most of the

patients. No comparison could be tried as none has presented the percentage of UTI. There was no evidence of multisystem disorder like SLE, Henoch Schonlein purpura, Amyloidosis etc. in cases of present study.

An attempt was made to study the seasonal incidence of disease. Table VIII depicts that maximum patients had onset or relapse of their illness in October-December (32.30%) followed by July-September (29.23%). So nearly two thirds of patients were seen in July-December. 21-53% cases were seen in January-March and the least in April-June (16.92%).

Not much workers have tried to establish any seasonal factor except Reeves et al (1975) and Meadow et al (1981). As there is history of URI and allergic rhinitis in patients of nephrotic syndrome, it was thought whether it has some relationship with allergens prevalent in particular season. Though Meadow et al (1981) could not relate seasonal factor to onset of nephrotic syndrome and found that onset was distributed throughout the year, they also observed that onset was less common in April, May and June (9%) which is similar to findings of present study. They noted highest incidence in July-September (32%). Overall their observation was similar to present study in this respect that onset is less in summer months and more in winter months. Reeves (1975) noted that seasonal nephrotic syndrome does occur. If at all there is some relationship, it needs further investigation regarding

correlation of seasonal pattern of pollen allergy, house dust, mites, because workers have noted serum IgE tends to be higher in these children.

Among 23 cases of group B patients, who had history of similar complaints in past also, it was observed that 52.17% cases had experienced once, 30.43% cases twice and 8.70% cases 2 or more relapses (Table IX).

By definition of nephrotic syndrome, serum albumin levels less than 2.5 gm% and serum cholesterol more than 200 mg% are part of diagnostic criteria. Though previous workers have observed fulfillment of above criteria in majority of patients, yet exact figures are not available for comparison. In patients with initial episodes, serum albumin levels were $\angle$2.5 gm% in 96.24% cases but rest also had low serum albumin levels.

Estimation of 24 hour urinary protein protein was done in each case and in 6.15% cases proteinuria was $\angle$ less than massive ($\overline{7}$150 mg/kg/day or $\angle\underline{=}$40 mg/m^2). Majority of patients had proteinuria in range of 100-150 mg/kg/day (43.08%). Only 21.53% cases had $\overline{7}$150 mg/kg/day proteinuria (Table XI).

Prasad et al (1980) reported massive proteinuria $\overline{7}$0.5 gm% in 57.1% cases and serum albumin levels $\angle$3.0 gm% in 57.1% cases. They observed serum cholesterol $\overline{7}$300 mg% in 74.2% cases while in present study, only 39% cases had serum cholesterol beyond 300 mg%.

Except for Prasad et al (1980) no worker had observed percentage of cases in different ranges. Low

serum albumin levels (⁄2.5 gm%) were observed in only 65.22% of cases. Serum cholesterol levels were raised in 92.86% of cases with initial episodes and 65.22% with relapse.

So in relapse cases, both clinical as well as biochemical derangements are less as compared with initial stage. This observation was not probably reported in literature.

In present study, raised blood urea levels ⁄40 mg% was observed in 18.46% of cases. Prasad et al(1980) had observed this figure to be 28.5%. While serum creatinine was found raised in 20% of cases in present study. Prasad et al (1980) observed these figures to be 14.4% cases. ISKDC reported this figure to be 15% in MCNS and Saxena et al (1988) in 28% of cases. Azotemia was transient in most of these cases.

As MCNS is known to be the commonest lesion in nephrotic syndrome in children, it was not advisable to perform renal biopsy in every patient.

Age more than 1 year or less than 6 years, absence of hematuria and azotemia response to steroids are characteristic features of MCNS. These patients (40) were 61.54% and (25) 38.46% cases were those who did not fulfil above mentioned criteria so they were selected for renal biopsy (Table XII).

Bernstein et al (1982) opined that renal biopsy is usually not indicated in children with steroid sensitive

nephrotic syndrome. It was policy of Mcdonald et al (1976) to do biopsies in those nephrotic syndrome children who were less than 1 or more than 6 years of age or who fail to respond to initial 2 weeks of cortico-steroid therapy. On above criteria they felt need to biopsy ⟨40% of the nephrotic children. Besides that we thought it necessary to undertake biopsy in patients who were relapsing frequently, had developed steroid toxicity and induction of cytotoxic drug therapy was being considered. With all above considerations in mind we ventured for percutaneous renal biopsy in 25 patients (38.46%) of our study group (Table XII).

MCNS was the commonest lesion even in cases with atypical presentation. Among 25 cases who were biopsied, 12 (48%) still turned out to be MCNS. Meadow et al (1981) who chose patients for biopsy on similar pattern reported that in 50% cases who were biopsied lesion was MCNS in rest biopsy was not under taken as they were unlikely to show histological lesion other than MCNS, because their clinical course and findings were even more typical of MCNS than those who underwent biopsy.

Overall minimal change nephrotic syndrome(MCNS) was lesion in 52(80%) cases. Among them 40 had typical clinical presentation while 12 were diagnosed after biopsy. Previous workers Habib et al (1971) and ISKDC (1978) reported it to be present in 52-78% of idiopathic nephrotic syndrome cases, while Saxena et al (1988) reported it in

68.3% cases. Other workers have reported it in 85% cases.

In the present study, mean age of MCNS cases was 5.49±2.65 years, almost similar to 5.2 years as reported by Saxena et al (1988) and 5.8 years as described by other workers. Hematuria was observed in 11.53% cases in the present study. Habib et al (1977) described it in 13 to 29% of cases while Rance et al (1976) observed it in 13% cases and Saxena et al (1988) in 40% cases. Gross hematuria was very rare , 1.1% observed by Cameroon (1978) and 1.4% as observed by Saxena et al (1988). 13.48% cases of MCNS in present study group turned out to be hypertensives as against 9% observed by Rance et al (1976). Habib et al (1971) and ISKDC (1978) described it in 6-13% cases and Saxena et al (1988) in 35.5% cases. But hypertension was mild and transient in majority of cases. Findings of present study are in accordance in of previous workers except Saxena et al (1988) in this regard. Azotemia was observed only in 7.69% of MCNS cases. Rance(1976) noted it in 4% cases. Saxena et al (1988) too observed normal mean values of blood urea and serum creatinine cases in MCNS.

As depicted in table XIII, focal glomerulosclerosis (FSGS) was found in 4(6.15%) cases. Marginally higher incidence (in 10%) was reported by Cotran et al (1983). Saxena et al (1988) observed FSGS lesion in 10.6% cases of their biopsies group of patients. Relatively

lower percentage of FSGS cases in present study can be explained by the fact that many FSGS patients responded to steroids favourably and so there is a possibility of including one or few with typical MCNS thereby avoiding consideration for biopsy. Besides this it is disputed by some workers whether it is a separate entity at all or not. In fact Churg et al (1970) brought this entity to light from those patients in which steroid response was relatively poor. Waldnerr (1983) is of opinion that it represents variation of MCNS rather than separate entity. Goldzer et al (1984) disputes whether FSGS represents a distinct disease or is simply a phase in evolution of a subset of patients with lipoid nephrosis. Patient showing MCNS in first biopsy may subsequently show focal segmental glomerulosclerosis (FSGS). Besides this as the lesion is focal and changes are present in juxta medullary glomeruli chances of missing some cases of FSGS on biopsy cannot be ruled out. Mean age observed for this group was 6.25 years which is little higher. Almost similar observations were also made by Saxena et al (1988) who noted mean age in FSGS to be 9.857 ± 2.795 years. Rance et al (1976) also observed the same. Rance et al (1976) observed hematuria in FSGS to be 66%. Cameroon (1968, 1973), Glasgow (1971), Nash et al (1976) also observed higher incidence of microscopic hematuria in FSGS (50-90%). Gross hematuria was not thought to be that common in this group. This is in accordance of the observation of hematuria in 50%

cases of FSGS in present study.

Hypertension was observed in 25% cases of FSGS in present study, while Rance et al (1971) had observed it in 10% of FSGS cases and Saxena et al (1988) observed it in 85.7% of cases. So observation of present study lies in between of these two extremes, but definitely hypertension was relatively common in FSGS as compared to MCNS.

Azotemia to be prevalent in more, was observed by almost all workers. Rance et al (1976) observed it in 10%, while Cotran et al (1983) observed it in 25% cases. Saxena et al (1988) ascertained significantly higher values of serum creatinine and blood urea in FSGS. Azotemia was observed in 50% cases of present study.

In fact importance of this lesion was relative lack of response to steroids and progression to end stage renal disease as described by Churg et al (1970).

Membranoproliferative glomerulonephritis was observed in 4(6.15%) cases in present study as against 10% by Cotran (1983). Saxena et al (1988) observed it in 13.6% cases. Mean age observed in present series was definitely higher 9.25 years as compared to 5.49$\pm$2.65 years of MCNS group. Saxena et al (1988) had observed mean of 9.556$\pm$1.740 years. Earlier workers have described it to be most common lesion in 2nd decade. Microscopic hematuria is very common and almost in all cases even gross hematuria is not rare. Rance et al (1971) noted gross hematuria in 20% and microscopic in 68% cases. In present series hematuria was present in all 4 cases of membranoprolifera-

- tive glomerulonephritis. Hypertension was present in 75% cases of membranoproliferative glomerulonephritis in present study while in 25% cases in study of Rance et al (1976) and in 88.8% in study of Saxena et al (1988).

In most of the cases of present study in membranoproliferative group, hypertension was not transient and required specific drug therapy.

Azotemia was common in membranoproliferative glomerulonephritis (50%) in present study as compared to 31% cases of Rance et al (1976).

In present study, 4.16% cases on light microscopic examination there was only slight diffuse increase in mesengial cells and cell matrix and thickening of mesengial shock. Capillary wall and interstitium was normal. This lesion was first described by Drunmond et al (1966), and well recognised by Churg et al (1970). Habib et al (1973) described this lesion in 2.5 to 5.3% of cases. Other workers also described it in 5% of cases. In present study, hematuria,hypertension and azotemia was present in 33.33% cases. Worekrs have described this lesion clinically indistinguishable from MCNS except for older mean age (White, 1970) and higher incidence of Hematuria. Brown et al (1979), Trainin et al (1975) described hematuria in 36 to 100% cases. It's close resemblance to MCNS have prompted workers to classify mild to moderate, mesengial proliferation as MCNS. Newman et al (1976) have said that some of these patients may

subsequently develop FSGS. Mean age in present study was 6.5 years as compared to 5.49±SD years of MCNS. In membranous nephropathy was present in 3.08% of present series, while Saxena et al (1988) reported it in 7.5% cases. Hematuria was commoner (50%) which is in accordance of other studies. Rance (1976) reported it microscopic hematuria in 70% and gross in 20%. Saxena et al (1988) reported hematuria in 60% of cases and hypertension in 60% cases as compared to present study 50%. Cotran et al described it in 15-35% cases. Mean age observed in present work was higher 9.25 years as compared to 5.49 years in MCNS and 7.6±1.941 years for same lesion by Saxena et al (1988). In this series azotemia was commoner (50%). Saxena et al (1988) also observed similar findings.

An attempt was made to study the pattern of response to steroids in correlation of histopathologic lesion. The response pattern was grouped in four categories.

Group B comprised non responders, group C frequent relapsers and group D included steroid dependent. Group A comprised responsive pattern other than above mentioned. Majority of them were responders and typical of MCNS type.

It was an endeavour to biopsy as many cases as possible with atypical steroid response, so that underlying pathology could be ascertained. Among non responder (Resistant) group all 6 cases were biopsied and among them

2 cases were of membranoproliferative and 1(16.67%) case of membranous variety. Prasad et al (1980) demonstrated minimal lesion in 20% cases of steroid non responders and mesengial proliferative lesion in 25% cases and membranous lesion in 20% cases and membranoproliferative lesion in 35% cases. Those findings are though not exactly but basically correlate with our findings. Trainin (1975) observed that 10% cases of MCNS would turn out to be steroid resistant, while in present series 2 out of 52 (3.85%) MCNS cases turned out to be non responders. In both of these caaes age of child was more than 7 years as observed by ISKDC (1981), that in all probability non responder cases if turns out to be of MCNS type on biopsy shall be more than 7 years age. 3 out of 4(75%) cases of membranous proliferative group were steroid resistant while 50% of membranous glomerulonephritis cases were steroid resistant. This high percentage of response in these groups was described by all previous workers but no any proven cases of FSGS could be found to be steroid resistant in the present study.

As ISKDC (1974) has described that 25% cases of MCNS will relapse frequently. In 10 out of 13 (76.92%) cases of frequent relapsers, biopsy was possible and out of those 10 cases 60% had minimal changes lesion while 20% each had FSGS and mesengial proliferative lesion. It has already been described that among frequent relapsers 50% cases were of minimal change disease.

According to our observation 50% cases of FSGS were relapsing frequently i.e. very high percentage and 2/3 cases of mesengial proliferative group were also frequently relapsing. Abramowicz et al (1970) and other workers had observed that many of biopsy proven FSGS cases will become frequent relapsers and steroid dependent and develop late steroid resistance. As we followed our patients for maximum 24 months, we were unable to ellicit late steroid resistance in FSGS cases. We could biopsy 4 out of 6 (66.67%) cases with steroid dependence and 2(50%) of them were MCNS and 25% each of FSGS and membranous type.

Immunological abnormalities in nephrotic syndrome are being analysed for long time. Reduced concentration of gammaglobulins in serum of patients with nephrotic syndrome was reported as early as 1940 (Longsworth, 1940). Subsequently decreased levels of IgG have been observed in patients of idiopathic nephrotic syndrome irrespective of the course (Giangiacoma, 1975). As evident from table XIV mean concentration of serum IgG 853.38± 276.53 mg/dl is lower as compared to control's 1777.50± 124.73 mg/dl and this is statistically highly significant ($p < 0.001$). IgG levels in nephrotic syndrome children were 48.01% that of controls.

Andal et al (1990) also reported low serum IgG levels at the onset ($p < 0.001$). They also observed 48% fall in serum IgG levels.

Mehta and Ali et al (1985) reported low serum IgG levels at relapse as well. In their study serum IgG levels were 576±164.1 mg/dl in cases and in controls 1072±34.85 mg/dl ($p < 0.001$). Yokoyama et al (1985) and Sudhir Gupte et al (1985) too reported low IgG levels. This depression in IgG cannot be explained on urinary losses alone. Increased catabolism may play a part. It has been postulated that T cell mediated conversion from IgM to IgG synthesis may be defective. It has not been established whether the depression in cell mediated immunity is a primary event or secondary to hypoalbuminemia, hyperlipidemia or zinc deficiency that co-exists in these patients as all these factors are known to depress cell mediated immunity.

In present study there was concomitant statistically significant rise in IgM levels. From 209.25±54.06 in controls to 300.57±72.01 mg/dl in nephrotic patients ($p < 0.05$). Significant rise in serum IgM levels was also reported by Sudhir Gupte et al (1985), Yokoyama et al (1985) and Andal (1990). Andal et al (1990) reported serum IgM levels to be 303.1±112.4 mg/dl in nephrotic syndrome versus 169.0±89.1 mg/dl in controls. In present study there was 143.6% elevation in IgG as compared to 163% observed by Andal et al (1990). Concomitant elevation of IgM with lowering of IgG may be related to the fact that nephrotic syndrome primarily a thymic cell dependent immune defect. Cells which normally produce IgM class of antibody

before converting to the synthesis of IgG and IgA fail to elicit response thus resulting in elevated levels of IgM (Davie et al, 1974). Similar observations were made in this present study.

In complement studies, there was no significant difference observed in levels of C_4 between nephrotic patients and controls while there was lowering in serum C_3 levels by 18%. They were observed to be 107.75 ± 35.39 mg/dl as compared to 130.25 ± 15.99 mg/dl in control group statistically insignificant ($p < 0.2$). The reason being that in MCNS serum complement levels remain normal by and large and majority of patients were of MCNS type in present study. Various workers have observed no changes in C_3 levels in MCNS.

Rance et al (1976) and Mehta and Ali (1985) reported that serum complement levels are generally normal in MCNS. Prasad et al (1980) reported initial hypocomplementemia in 9% of their MCNS children but in none of them it was persistently low. As obvious by table XV, 7.7% MCNS children had initial hypocomplementemia and similarly none of them had persistently low levels. Overall 20% children had initial hypocomplementemia as compared to 32% observed by Prasad et al (1980). In the present study persistently low levels were observed in 6.15% cases as compared to 8% of their. In present series all 4 children with membranoproliferative lesion had hypocomplementemia in the beginning and persistent in 75% children. Rance

et al (1976) reported hypocomplementemia in 68% cases of MPGN and Prasad et al (1980) reported initial hypocomplementemia in 83.3% children and persistent hypocomplementemia in 50% cases of MPGN.

In mesengial proliferative group Prasad et al (1980) observed hypocomplementemia in 87.5% cases and persistent in 12.5% of them, while in present work, initially low levels were observed in 66.67% cases and persistently low levels in 93.3% cases. Saxena et al (1988) too observed hypocomplementemia in all MPGN cases. In focal and segmental glomerulosclerosis and membranous nephropathy none of the patients had persistently low C_3 levels though few had initially low levels as observed in present study.

West (1965) and Ogg (1968) suggested that persistent hypocomplementemia is characteristic of a discret group of patients with poorly selective proteinuria.

In 4 patients of MCNS who had initially low C_3 levels. Two turned out to be steroid dependent and 2 developed late steroid resistance so low C_3 levels observed in MCNS can be related with altered steroid response later. None of the low C_3 level cases of MCNS suffered frequent relapsers.

Thus the measurement of serum levels of specific components of complement system is helpful in the diagnosis of 6 various types of nephropathies and in evaluation of therapy.

It was also tried to study the incidence of tuberculosis in nephrotic syndrome (Table XVII) and further analysis whether this has any bearing with steroid response pattern. This was thought necessary as tuberculosis infection is widely prevalent in our set up. and it has already been proved by Mclean et al (1977) and Vaishnav et al (1983) and other workers that presence of active though subtle infection may be responsible for steroid resistance in MCNS and even relatively slow response.

Twelve (18.46%) cases of present study group had evidence of primary complex. This was considerably higher than incidence of tuberculosis in children described as 2.7% by Dingley (1976). Vaishnav et al (1983) had observed evidence of tuberculosis in 10% of their group of nephrotic syndrome children while Prasad et al (1980) had described it in 35.38% cases before therapy and 10% cases after therapy so our incidence lies between these two and it is definitely higher than usual population, cause of which is to be ascertained. Among our patients with pulmonary tuberculosis/primary complex 66.67% cases had not received steroids earlier, indicating that this higher incidence of tuberculosis was not mainly due to flaring up of hidden tuberculous focus during therapy.

Further an attempt was made to elicit possible effect on steroid response, as shown in table XXIII. Patients of present study were divided into two groups.

Group A (patients responding within 2 weeks which had incidence of tuberculosis in 8.7%) and group B (patients responding after 2 weeks) which had incidence of tuberculosis in 33.33%) which indicated that presence of chronic infection like tuberculosis should be searched in patients who showed relatively slower response to steroids. It has been already discussed that presence of infection can result in slow or no response to steroids. Among frequent relapsers incidence of tuberculosis (23.07%) was little higher than in our whole study group (18.46%) which does not seem to have any bearing. So it can't be said whether frequent relapsers have any relation with underlying tubercular infection. Vaishnav et al (1983) have also correlated slow response to steroids with underlying tubercular infection but difference between the two studies is that they had taken slow responders as who respond after 8 weeks as compared to two weeks in the present study.

In 96.92% cases of present study steroid was used for induction of remission while in rest (3.08%) it was achieved spontaneously (Table XVIII). For maintenance of remission steroids were used in 68.25% cases of present study while in 31.75% of cases this was not required. Cyclophosphamide was used in 12.31% cases for induction and in 12.50% cases for maintenance of remission in the present study.

Though spontaneous remission is described in cases of membranous nephropathy, percentage was not observed previously.

Different patterns of steroid response have been described by various workers and ISKDC. We had endeavoured to group our patients in these categories and compared them with previous workers observations (Table XIX). Out of 65 cases, 2(3.08%) achieved remission spontaneously and among rest 63 cases, 96.92% were initial responders. These were the patients who responded during first 8 weeks of steroid therapy.

3.17% cases were early non responders while 6.15% cases turned out to be late steroid non responder.

Trainin (1975) observed that 5-10% cases of MCNS are early non responders while 5% turn out to be late non responder. Lesions with focal glomerulosclerosis and mesengial proliferative are known to develop late steroid resistance. Grupe (1979) estimated late steroids resistance in 4.8% and Srivastava et al (1986) in 3% cases. Six cases (9.23%) of our study were steroid dependent.

Abramowicz et al (1970) has ascertained that more cases of FSGS will become steroid dependent but percentage has not been described.

Slow responders are that group of patients in whom proteinuria become less but did not disappear within 8 weeks of steroid therapy, though eventually disappears completely (Vaishnav et al, 1983).

An attempt was made to group the patients according to response time, which is the interval between the initiation of treatment and first day of traces or nil reaction for urine albumin.

But as under our observation majority of cases (75.40%) respond within 2 weeks of initiation of steroid therapy. So we have used the term 'relative slow responder' in which those patients were included who responded after 2 weeks of steroid therapy.

Twenty percent of our cases were frequent relapsers, while in ISKDC (1978) 25% children of MCNS are said to be frequent relapsers and this percentage is still higher in focal glomerulosclerosis group in our study it was 11.53% cases of MCNS were frequent relapsers (all biopsy proved) and 50% cases of FSGS were F.R. (biopsy proved).

75.40% cases responded within 2 weeks of steroid therapy among these 22.95% responded within 1 week and 52.45% between 1-2 weeks (Table XX). It has been described in previous studies also that most of the children begin to respond to corticosteroid regimen within 14 days of treatment (Mc Enery et al, 1982).

According to ISKDC (1976) all nephrotic children who were going to to respond to prednisolone 73% did so within 14 days and another 21% in next 14 days of initial steroid therapy.

In this study 8.19% cases responded between 3-4 weeks and 3.28% cases responded between 4-5 weeks and 1.64% cases responded between 5-8 weeks of initiation of steroid therapy. So over all 24.60% cases were labelled as relative slow responder by us. None of the previous workers have classified their cases in this fashion.

It was tried to estimate relapse free interval after remission was induced by steroids or cyclophosphamide (Table XXI and XXII).

Relapse free interval was <2 months in 6.15%, 2-4 months in 10.77%, 4-6 months in 18.46% and 6-12 months in 21.54% and 12-24 months in 36.92% cases. So maximum patients (24) were free from relapse for 1-2 years after remission was induced but more than 2 years relapse free period was present in only 6.15% cases as our study period was only 24 months, we estimated these figures by retrospective figures also. None of previous workers have studied response to steroids in this way, except that they described that majority (90%) of MCNS cases suffer relapses and 25% of them frequently (ISKDC, 1974). Similarly among 8 cases in which cyclophosphamide therapy was administered, 2 were free from relapses for <6 months and 2 for 6-12 months and 4 (50%) for >1 year. Previous studies have also described longer remission on cyclophosphamide therapy. Sixty five percent patients have been estimated to remain in remission for more than 5 years and in 50% cases permanent remission was noted. Due to

short study period we could not corroborate these observations. (Chiu et al (1973). Moncrief (1969) showed that 25% children did not had a relapse within 1 year of treatment as compared to 50% in our observations and 50% did not relapse for 2 years.

Early identification of frequent relapsers has always posed problems. Attempts to correlate prediction of frequent relapsers with hematuria, hypertension and azotemia have not been useful and attempts to correlate course of the disease with the histologic findings have met with only limited success. So we attempted to review a report of ISKDC (1982) in which number of relapses in first 6 months of onset was correlated with future course of disease. We observed that among patients who did not suffer any relapse in first 6 months (44.61%) only 3.45% developed frequent relapses while among 6.15% patients with $\bar{7}3$ relapses in first 6 months 50% had frequent relapses in subsequent course (Table XXIV). ISKDC (1982) underlined absence of a relapse during first 6 months - the initial response proved to be an excellent clinical predictors of a favourable course during the first 2 years. Occurrence of $\bar{7}3$relapses during initial 6 months period can be used clinically to predict a frequently relapsing course.

Various types of steroid response in nephrotic syndrome have already been discussed and also their correlationship with histopathologic lesion. In table XXV an attempt was made to correlate steroid response with clinical features.

In children ⟨6 years age 22% patients were frequent relapsers, while resistant (2.27%) and dependent (6.82%) cases were less. In contrast to this resistant (23.08%) and dependent cases (14.29%) were common in age group ⟩6 years and frequent relapsers were slightly less (14.28%). Hypertension and hematuria and azotemia were more commonly associated with steroid resistance, but not with steroid dependency.

Cases were followed up carefully to study response pattern and relapses and number of patients registered suffered relapses during 2 years study period and in these episodes of relapses we observed history or evidence of URI in 28%. Allergic episodes like allergic rhinitis in 21%, UTI in 4%, other infections in 7%. In 40% cases none of the above or known factor was there. URI and allergic episodes are already been discussed as possible factors having patential bearing over occurrence of relapse as also seen by Meadow et al (1981). They also observed like us that a nasal discharge was a frequent precursor or accompaniment of nephrotic syndrome. Meadow (1981) observed that 50% patients had history of at least

relapses twice within 3 days of such URI. In 50% patients relapse was always associated with a cold. In some cases history suggestive of communicable viral cause was elicitable.

Though in our study group this observation had not as high incidence as of Meadow et al (1981) but it was still significantly higher to think on same lines. The difficulty was that despite carefull questioning no provocative factor could be found to account for runny nose. It was interesting that runny nose was not common in children who had single bout of nephrotic syndrome. As raised IgA levels are also known in nephrotic syndrome patients this would lead to identification of certain factors, if avoided could lead to decrease in relapses or development of preventive measures or drugs.

As shown in table XXVII, we have been able to establish very low levels of serum IgG levels (531.38$\pm$ 132.87 mg/dl) at onset in frequent relapsers as compared to 938.07$\pm$250.30 mg/dl in infrequent relapsers and this difference was statistically highly significant($p < 0.001$).

Infrequent relapsers were also having highly significant low levels of IgG as compared to control group ($p < 0.001$). This observation was in accordance with Andal et al (1990) who had noted the same in their study. But in present study serum IgM levels were significantly higher in frequent relapsers as compared

to infrequent relapsers($p < 0.05$), while Andal et al had though observed higher IgM levels in frequent relapsers but this elevation was not found statistically significant. So, very low IgG and high IgM levels can serve useful predicting marker for frequent relapsers though Giangiacoma (1975) reported no change in immunoglobulin levels between frequent and infrequent relapsers.

SUMMARY

AND

CONCLUSION

SUMMARY AND CONCLUSION

The present study was conducted in the department of Paediatrics, M.L.B. Medical College, Hospital, Jhansi over a period of two years from August, 1991 to July, 1993.

The study was primarily aimed to evaluate the clinical profile of nephrotic syndrome along with biochemical, pathological and immunological changes that take place along with the disease process. A total of 65 cases of nephrotic syndrome were examined in the present study.

AGE, SEX AND SEASONAL INCIDENCE

Incidence of nephrotic syndrome, of total paediatric admission was observed to be 1.62%. Nephrotic syndrome comprised of 72.2% of children presenting with renal disease in duration of this study. Male : female ratio was 1.8 : 1. Highest incidence was observed in age group of 4-6 years (41.53%), nearly 2/3rd cases were between age group 1-6 years. In none of the child positive family history was elicited.

Maximum incidence was observed in between October-December (32.30%) followed by 29.23% in July-September. Two third cases were observed between July-December. So there was definite preponderance of cases in latter half of the year.

In present study group 23(35.39%) cases had suffered one or more episode while 42(64.61%) cases were having first episode of the illness.

CLINICAL FEATURES

Oedema was observed in 93.85% cases overall while in 100% patients with initial episode and 82.61% in cases with relapse.

Oliguria was present in 88.09% in cases with initial episode and 73.91% in patients with relapse. Gross hematuria was present in 6.15% of cases.

RELEVANT PAST HISTORY

URI was found in 14.29% cases with initial episode and 39.13% in cases with relapse.

History of allergic episode like rhinitis was present in 4.76% cases with initial episode while in 17.39% cases with relapse. Of the 23 cases (35.37%) who came in relapse 12(52.17%) cases had suffered one, 7(30.43%) cases had suffered two and 2(8.70%) cases each had suffered three or more than 3 previous episodes.

IMPORTANT CLINICAL FINDINGS AND HISTOPATHOLOGICAL CORRELATION

a. Hypertension

It was observed in 13(20%) cases of which 7 (53.85%) had minimal change glomerulonephritis, 3(23.08%) had membranoproliferative glomerulonephritis and 1(7.7%) each had focal segmental glomerulosclerosis and mesengial

proliferative and membranous nephropathy.

13.46% cases of MCNS, 25% cases of focal segmental glomerulosclerosis, 75% cases of membranoproliferative, 50% cases of membranous nephropathy and 33.33% cases of mesengial proliferative nephropathy had hypertension of various grades.

b. Hematuria

Of the total 14(21.54%) cases which had hematuria 6(42.86%) were having MCNS, 2(14.23%) were having FSGS, 4(28.5%) membranoproliferative and 1(7.15%) each had membranous and mesengial proliferative glomerulonephrosis.

Hematuria was observed in 11.53% cases of MCNS, 50% cases of FSGS, 100% cases of membranoproliferative glomerulonephritis, 50% cases of membranous nephropathy, and 33.33% cases of mesengial proliferative nephropathy.

c. Azotemia

Azotemia was observed in 10(15.38%) cases, of which 4(40%) had MCNS, 2(20%) cases each had FSGS and membranoproliferative and one (10%) case each had mesengial proliferative and membranous nephropathy. In MCNS group 7.69%, in FSGS and membranous proliferative and membranous group (50%) each and in mesengial proliterative nephropathy 33.3% cases had azotemia.

d. UTI, Anemia, Hepatomegaly, Multisystem Disorders

Of our study group, 15.38% cases had evidence of UTI, 73.84% had anemia of variable degrees and 43.07%

cases had evidence of hepatomegaly. None had evidence of any multisystem disorders.

e. Ascites and Pleural effusion

While 50.77% cases had evidence of ascites, only 3.08% cases had evidence of pleural effusion.

BIOCHEMICAL CHANGES

Blood urea levels were raised in 18.46%. Raised serum cholesterol levels (7200 mg%) were observed in 83.08% cases while low serum albumin levels (∠2.5gm %) were observed in 84.62% cases.

61(93.84%) cases had 24 hour proteinuria of massive degrees, 750 mg/kg/day.

HISTOPATHOLOGICAL CHANGES

Of total 65, 40(61.54%) cases had no evidence of hematuria, hypertension or azotemia and responded favourably to steroids and had age on lower side (∠7 years) were labelled clinically as having typical minimal change lesion. Rest 25(38.46%) cases were selected for percutaneous renal biopsy. Out of these 12 cases (48%) still turned out to be having MCNS. Thus in all 52 cases (80%) were having nephrotic syndrome of minimal type, 4(6.15%) cases had membranoproliferative glomerulonephritis, 3(4.16%) cases had mesengial proliferative glomerulonephritis and 3(3.07%) cases turned out to be of membranous type. Mean age in MCNS lesion was 5.49±2.65 years while it was 6 years in FSGS, 9.25 years in membranoproliferative

group, 6.35% years in mesengial proliferative and 7.5 years in membranous nephropathy. Profile of hematuria, hypertension and azotemia has already been summarised.

IMMUNOLOGICAL CHANGES

Mean serum IgG levels were 853.38±276.53 mg/dl in nephrotic group as compared to 1777.50 mg% in controls. This lowering was statistically quite significant($p < 0.001$). Simultaneously mean serum IgM levels were raised in nephrotic group ($p < 0.05$).

Initial hypocomplementemia was observed in 7.7% cases of MCNS and 2.5% in glomerulosclerosis and in all cases of membranoproliferative glomerulonephritis, 50% cases of membranous nephropathy. Persistant hypocomplementemia was observed mainly in membranoproliferative group only.

DRUGS USED FOR REMISSION

In 96.92% cases steroids (Prednisolone 2 mg/kg/day) was used to induce remission and in 31.75% of them for maintenance of remission.

Cyclophosphamide was used to induce remission in 12.31% cases and to maintain it in 12.5%of them.

RESPONSE TO STEROIDS : CLINICAL CORRELATION

On alternate day steroid regimen, it was observed that 61(96.82%) cases were initial responders, 2(3.17%) cases were early non responders and 4(6.35%) cases were late non responders. Overall 9.52% cases turned out to be

resistant. 6 cases (9.52%) were steroid dependent while 15 cases (24.60%) responded relatively slowly (after 2 weeks), 20% cases were frequent relapsers (8.2% of them dependent on steroids) and 50 cases (81.97%) cases were infrequent relapsers, while in age group of ⁄6 years 22.72% cases were frequent relapsers, 2.27% were resistant while 6.82% were dependent to steroids. In age group 76 years, 14.28% cases each were frequent relapsers and resistant cases were 23.81 %.

STEROID RESPONSE AND UNDERLYING PATHOLOGIC LESION

Of the 13 frequent relapsers, 10 were biopsied and 60% of them were of MCNS type, 20% each of FSGS and mesengial proliterative type.

Of 4 biopsied steroid dependent cases, 2 were having minimal change and one each had focal glomerular and membranous changes.

Of 6 biopsies non responders, 2(33.33%) were having minimal change nephrotic syndrome and 3(50%) were of membranoproliferative type while 1 case had membranous nephropathy.

TIME TAKEN TO RESPONDE TO STEROIDS

14 cases (22.95%) responded within 7 days of start of steroid in daily doses while majority of them 32 (52.45%) cases responded within 1-2 weeks of therapy in all approximately 75.40% cases responded within 15 days. Rest 24.60% cases were relatively slow responders. 11.47% cases responded between 2-3 weeks, 8.2% between 3-4 weeks,

3.28% between 4-6 weeks and only one 1.64% between 6-8 weeks.

RELAPSE FREE INTERVAL

On steroid therapy it was less than 2 months in 6.15% cases, 2-4 months in 7(10.77%) cases, 4-6 months in 18.46% cases, 6-12 months in 21.54% cases while 36.92% cases had relapse free interval of more than 1 and less than 2 years, only 6.15% cases had it more than 2 years.

ON CYCLOPHOSPHAMIDE THERAPY

Relapse free interval of 0-6 months and 6-12 months was observed to be in 25% cases and more than one year in 50% cases.

ASSOCIATION OF TUBERCULOSIS AND
AND ITS EFFECT ON STEROID RESPONSE

Of our total study group 18.46% cases had evidence of primary complex. In relatively slow responders (72 weeks duration), 33.33% cases were having evidence of tuberculosis as against 8.70% cases in those responding quickly (<2 weeks duration).

RECOGNITION OF FREQUENT RELAPSERS

An attempt was made to evaluate markers for early recognition of frequent relapsers. Clinical presentation and histopathological changes provided no correlation.

It was seen that in cases having more than three relapses in first 6 months - 50% of them had 2 and 50% of them had ≥ 3 relapses in subsequent 6 months, while in group having no relapse in first 6 months, only 6.9% cases had 2 and 3.45% cases had ≥ 3 relapses in subsequent 6 months. So higher incidence of relapses in first 6 months correlated with occurrence of frequent relapses in subsequent 6 months.

By immunological studies it was seen that in cases those who relapse frequently serum IgG levels were very low 531.38 ± 132.07 mg/dl as compared to 938.07 ± 250.30 mg/dl in those who relapse in frequently ($p < 0.001$). Concomitantly serum IgM levels were raised significantly ($p < 0.05$) in frequent relapses as compared to infrequent relapsers.

It was also observed that in 49% cases of relapse evidence of upper respiratory tract infection and allergic rhinitis was present. In contrast to this such history was not elicitable in those who relapsed infrequently.

CONCLUSION

Following conclusions could be drawn from the present study :-

1. Males were predominantly affected as male : female ratio was 1.8 : 1.
2. Two third of the cases were observed between age group 1-6 years.
3. Definite preponderance of cases in later half of the year. (July - December)
4. While one out of every five cases showed hypertension, it was most frequently present in membranoproliferative group followed by membranous nephropathy & focal glomerular sclerosis was least common in Minimal lesion group.
5. Hematuria was also present in one fifth of cases, but was present in all cases of membranoproliferative group and least in MCNS group.
6. 61.54% cases behaved clinically as typical minimal lesion type. In all 80% cases were having MCNS, 6.15% had membranoproliferative glomerulonephritis and FSGS each, 4.16% had mesengial proliferative and 3.07% cases had membranous nephropathy.
7. Mean age was observed to be highest in membranoproliferative glomerulonephritis followed by membranous nephropathy, mesengial proliferative, focal glomerular sclerosis and was least in MCNS.

8. Mean serum IgG levels were significantly low while mean serum IgM levels were significantly raised in nephrotic group as compared to controls. Though mean serum C_3 levels were also found to be low but not statistically significant.
9. Initial and persistent hypercomplementemia was mainly observed in membranoproliferative group.
10. While majority of cases responded to steroids initially , three fourth of cases responded within 2 weeks of initiation of steroid therapy. Rest one fourth cases were relatively slow responders.
11. Among slow responders incidence of tuberculosis was much higher than the rest.
12. Correlation was observed between frequent relapsers and cases having more relapses in first 6 months, cases having very low IgG levels and higher IgM levels at onset and cases having history or evidence of URI or allergic rhinitis.

BIBILIOGRAPHY

BIBLIOGRAPHY

1. Abramowicz, Barnett HL, Edelmann CM et al. Controlled trial of azathioprine in children with nephrotic syndrome. Lancet, 1970; 1 : 959.

2. Adhikari M, Coovadia HM, Loening AWEK. The nephrotic syndrome in children. S Afr Med J, 1976; 50: 39-45.

3. Adler AJ, Lundin AP, Fernroth MV et al. B thromboglobulin levels in the nephrotic syndrome. Am J Med 1980; 69 : 551.

4. Ae Mouzone Cambon A, Baulsson F, HL ADR in children with idiopathic nephrotic syndrome. Tissue antigens 1981; 17 : 518-523.

5. Agnes Fogo, Edith P, Hawkins, Philip L Berry, Alan D, Glick, Myoa L Chiang, Robert C. MacDonell Jr and Iekuni Ichikana. Kidney Int, 1990; 38 : 115-123.

6. Alain Meyrier et al. Remission of idiopathic nephrotic syndrome with cyclosporin A. Br Med J 1986;292:789-92.

7. Amir Tejani, Kishore Phadke. Anthony Nicastic, Orlando Adamson CK Chen, Howard Traohtman, Cena Tejani. Efficacy of cyclophosphamide in steroid sensitive childhood nephrotic syndrome with different morphological lesion. Nephron 1985; 41 : 170-173.

8. Andal A, Chellani H, Anand NK, Chandra M. Immunoglobin profile in frequently relapsing nephrotic children. Indian Pediatric 1990; 27 : 1045-49.

9. Andrews PM. Glomerular epithelial alterations resulting from sialic acid surface cor removal. Kidney Int, 1979; 15 : 376.

10. Anne Margret Wingen Dirk and Muller Wiefel and Kurl Scharer. Comparison of different regimens of prednisolone therapy in frequent relapsing nephrotic syndrome. Acta Pediatrics Scan 1990; 79 : 305-310.

11. Arbeitsgemeinschaft fur Padiatrische Nephrotgie. Alternate day prednisolone is more effective than intermittent prednisolone in frequently relapsing nephrotic syndrome. Eur J Pediatrics,1981;135:229-37.

12. Ariela Benigni Gian Franco Rizzoni Alberto Antotini, Antonells Piccinelli Giusseppe Remuzzi : Preliminary report. Renal T(A_2) Systheti in children with frequent relapsing NS. Lancet, 1990; 336 : 533-34.

13. Awadalla MB, Teebi AS, Elzoki AY and Shaltout A. Frequent relapses MC nephrone : an unrecognised X-linked disorder. Eur J Pedt 1989; 149 : 205.

14. Baluarte HJ, Hiner L, and Gruskin AB. Chlorambucil dosage in frequently relapsing nephrotic syndrome. A controlled clinical trial. J Pediatr 1978;92:295.

15. Barakat AY, Birbari AE, Derkalollstan VM, Muffarrij AA. The kidney in genetic diseases. New York, Churchill Living stone, 1986; 32-36.

16. Barratt TM and Macauley D. Renal disease in childhood in Black Dak (Ed.) : Renal Disease, Edition, 3 Oxford England Blackwell Scientific Publications, 1972:812.

17. Baxter JM, Goodman HC and Havel RJ. Serum lipid and lipoprotein alterations in nephrosis. J Clin Invest, 1960; 39 : 455.

18. Bernard DV. Metabolic abnormalities in NS : Pathophysiology and complications. NS in contemporary issues in nephrology. Berry M Brenner and Jay H. Stein (eds.), 1982; 9 : 85.

19. Bernstein J Jr, Edelmann EC Jr. MCNS : Histopathology and steroid responses. Arch Dis Child, 1982; 57 : 816.

20. Bhandari B, Mandowara SL. Lipoprotein profile in nephrotic syndrome. Indian Pediatr, 1980;16 : 416-9.

21. Blan EB and Haas DE. Glomerular stalic acid and proteinuria in human renal disease. Lab Invest, 1973; 28 : 477.

22. Birmingham statistics. Birmingham City Council, 1983.

23. Bohlin AB and Berg U. Renal sodium handling in minimal change nephrotic syndrome. Arch Dis Child, 1984; 59 : 825-30.

24. Bohrer, Dean WM, Robertson CR et al. Influence of molecular configuration in the glomerular filtration of macromolecules. Kidney Int., 1978; 14 : 751.

25. Brenner BM, Stein JH. Contemporary issues in nephrology Vol 9, New York Churchill Living Stone, 1982; 145-167.

26. Brodehl J, Krohn HP, Ehnich JHH. The treatment of minimal change nephrotic syndrome (lipoid nephrosis) Cooperative studies of the Arbeitsegmeinschaft fur Pediatrische Nephrologie (APN) Klin Pediatrics, 1982; 194 : 162-165.

27. Bzojeren M, Over weight children. Acta Pediatr, 1952; 51 (Supple : 132).

28. Callis L, Nieto J, Vila A et al. Chlorambucil treatment in minimal lesion nephrotic syndrome. A reappraisal of its gonadal toxicity. J Pediatr 1980;97:653.

29. Carvello T, Johnson MP. Immunopathologic study of MCNS with mesengial IgM deposits.

30. Chang RLS, Deen WM, Robertson CR et al. Selectivity of the glomerulo capillary wall III. Restricted transport of polyanions. Kidney Int., 1975; 8 : 212.

31. Churg J, Habib R, White RHR. Pathology of the nephrotic syndrome in children. A report of ISKDC, Lancet, 1970; 1 : 1299-1302.

32. Churg et al : Pathology of the nephrotic syndrome in children. A report for ISKDC. Lancet, 1970; 1:1299.

33. Clara C, Laguernela, Thomas L, Buettner, Barbara R, Cole, Johu M, Kissane and Alan B Robson's. Kidney Int, 1990; 38 : 145-150. HLA extended Halohyper in steroid sensitive nephrotic syndrome in childhood.

34. Cotran RS and Rennke HG. Anionic site and mechanisms of proteinuria. N Eng J Med 1983; 309 : 1050.

35. Date V, Kaushik RV, Ali U, Mehta KP. Urinary concentrating capacity in patients with nephrotic syndrome. Indian Pediatr 1990; 27 : 1094.

36. Davidson AM, Camson SS, Kerr NS. The natural history of renal function in untreated idiopathic membranous GN in adults. Clin Nephrol 1984; 61-67.

37. Davie JM, Paul WE. Role of T lymphocytes in humoral immune response. J Immunol, 1974; 173 : 1438-45.

38. Deen WM et al. The glomerular barrier to macro molecules. Theoretical and experimental consideration : In Brenner BM and Stein JH(Eds) Nephrotic syndrome. Contemporary issues in nephrology, 1982;9 NewYork, Churchill Living stone.

39. Dingley HB. Tuberculosis in India (Editorial) Indian Pediatrics, 1976; 13 : 879-80.

40. Drummond KN. Minimal change nephrotic syndrome. In Behrman RE, Vanghan VE eds. Text book of Pediatrics, Philadelphia : W.B. Saunders, 1983; 1325-7.

41. Eisen HN. Antibody formation(Immunology). In Immunology, microbiology, 2nd ed. Edavis BD, Dulbecco R, New York Harper and Row, 1973; 349-624.

42. Fahey JL and Mckelvey EM. Quantitative determination of serum immunoglobulins in antibody agar plates. J Immunol 1965; 94 : 84-90.

43. Feehally J, Beattie TH, Brenchley PEC ET al. Modulation of cellular immune function by cyclophosphamide in children with minimal change nephropathy. N Eng J Med, 1984; 310 : 415-20.

44. Feehally JY, Kendall NP, Swift PGF and Walls J. Arch Dis Child, 1985; 60 : 1018-1020.

45. Fodor P, Saitua MT, Rodsignez E. Gonzalez B, Schlesinger L. T cell dysfunction in MCNS of childhood. Am J Dis Child, 1982; 136 : 713.

46. Forquhar MG et al. Current knowledge of functional architecture of the glomerular basement membrane. In Kucho R et al (Ed.) New Trends in Basement membrane research New York Raven Press, 1982; 57-71.

47. Frederic C, Strife MD, Elizabeth C, Jackson MD. Effect of NS or concentration of serum complement components. Am J Kidney Dis, 1986(1):VIII : 37-42.

48. Garin EH, Pryor ND, Fennell RS et al. Pattern of response to prednisolone in idiopathic minimal lesion nephrotic syndrome as criterion in selecting patients for cyclophosphamide therapy. J Pediatr 1978;92:304.

49. Gerald S, Arbus, Poncell S, Godfrey S, Bacheyie and Reubena Baumal. Focal segmental glomerulosclerosis with idiopathic nephrotic syndrome. Three types of clinical responses.

50. Giangiacomo J, Leary TG, Cole BR et al. Serum immunoglobulins in the nephrotic syndrome. A possible cause of minimal change nephrotic syndrome. N Engl J Med, 1975; 293 : 8.

51. Glassock RJ, Adler SG, Wond HJ, Cohen AH. Primary glomerular disease. In : kidney - 2nd edition. Eds Brenner BM, rector FC, Philadelphia, WB Saunders 1986; 929.

52. Grossong T, Mendelson L, Mondoza S et al. Serum IgE in patients with MCNS. Indian Pediatr,1973; 83 :767.

53. Grupe WE. Primary nephrotic syndrome in childhood. In : Barners LA ed. Advances in Pediatrics Vol 26, Chicago year book, 1979; 163-207.

54. Grupe WE, Makker SP and Pagelfinger JR. Chlorambucil treatment of frequently relapsing nephrotic syndrome. N Eng J Med, 1976; 295 : 746.

55. Gupta S, Yuceoglu AM. Immunological profile in children with MCNS. Acta Pediatr Scand 1985; 74:726-32.

56. Habib R, Klinknecth C and Gubler MC. Extra membranous glomerulonephritis in children. Report of 50 cases. J Pediatr, 1973; 82 : 754.

57. Habib R. Focal glomerular sclerosis (Editorial). Kidney Int, 1973; 4 : 355.

58. Habib R and Klein Knecht C. The primary nephrotic syndrome of childhood: classification and clinicopathological study of 406 cases. In Sommer SC (ed) Pathology Annual New York Appleton Century crofts., 1971; 417.

59. Habib R, Klein Knecht C, Gubler MC et al. Idiopathic membranoproliferative glomerulonephritis in children. Report of 105 cases. Clin Nephrol 1973; 1 : 194.

60. Hayslett JP, Krasser LS, Brensch KS, Kastigarian M. Epstein FH. Progression of lipoid nephrosis to renal insufficiency. N Eng Med, 1969; 281 : 181-86.

61. Hayslett JP, Kashgarian M, Bensch KG et al. Clinicopathological correlations in the nephrotic syndrome due to primary renal disease. Medicine, 1973;52:93.

62. Herdman RC, Michael AF, Good RA. Postural proteinuria Response to corticosteroid therapy. Ann Int Med, 1966; 65 : 286-289.

63. Honser M. Assessment of proteinuria using random routine samples. J Pediatr 1984; 104 : 945-8.

64. Hoyer JR. Idiopathic NS with minimal glomerular changes. In contemporary issues in nephrology. Brenner BM and Stein JH. Churchill Living stone, 1982; 145.

65. Hokoyama H et al. Immunodynamics of MCNS T and B lymphocyte subsets and serum immunoglobulin levels. Clin Exp Immunol 1985; 61 : 601-7.

66. Hulme B and Hardwicke J. Human glomerular permeability of macromolecules in health and disease. Clin Sci, 1968; 3(1) : 515.

67. H. Yoko Yama H, Kida H, Tani Y. Immunodynamics of minimal change nephrotic syndrome in adults T and B lymphocyte subsets and serum immunoglobulin levels. Clin Exp Immunol 1987; 61 : 601-607.

68. ISKDC. Early identification of frequent relapses among children with MCNS. J Pediatrics, 101(4):514-18.

69. ISKDC. Nephrotic syndrome in children. Prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. Kidney Int, 1978;13:159-65.

70. ISKDC. Prospective controlled trial of cyclophosphamide therapy in children with the nephrotic syndrome. Lancet, 1975; 11 : 423-27.

71. ISKDC. Nephrotic syndrome in children. A randomised trial comparing two prednisolone regimens in steroid responsive patients who relapse early. J Pediatr, 1979; 95 : 239-43.

72. Jing Fur Hu, Yu Zhi Liu. Elevated serum IgE levels in children with NS, a steroid resistant sign. Nephron, 1990; 54 : 275.

73. Jorge Joven, Cartor Villabona et al. Abnormalities of lipoprotein metabolism in patients with the nephrotic syndrome. New Eng J Med, 1990; 323 : 579-84.

74. Kaplan BS, Bureau MA and Drummond KN. The nephrotic syndrome in the first year of life. Is a pathologic classification possible. J Pediatr, 1979; 85 : 615.

75. Kauffman RH, Veltkamp JJ, Van Tilbury Vas ES.LA. Acquired antithrombin III deficiency and thrombosis in nephrotic syndrome. Am J Med, 1978; 65 : 607.

76. Kendall AG, Lohmann RC, Dossetor JB. Nephrotic syndrome and hyper coagulable state. Arch Int Med, 1971; 127 : 1201.

77. Klamperer MR, Gotoff SP, Alper CA, Levin AS and Rosen FS. Pediatrics, Springield, 1965; 35 : 765.

78. Lagrue G, Kherenmont S, Branellee A et al. Lymphokines and nephrotic syndrome. Lancet, 1975; 1 : 721.

79. Lewis EJ, Carpenter CB, Schur PH. Serum complement component levels in human glomerulonephritis. Ann Intern Med, 1971; 75 : 555-60.

80. Levinsky RJ, Malleson PN, Barratt TM et al. Circulating immune complexes in steroid responsive syndrome. N Eng J Med, 1978; 298 : 126.

81. Likata K and West CD. A serum inhibitor of blastogenesis in idiopathic nephrotic syndrome transferred by lymphocytes. Clin Immunol Immunopathol 1979; 12: 62.

82. Lilenfield AM, Lilenfield DE. Foundations of epidemiology. Oxford University Press, 1980.

83. Long JC, Hall CL, Brow CA et al. Binding of soluble immune complexes in serum of patients with Hodgkins disease to tissue cultures derived from tumor. N Eng J Med 1977; 297 : 195.

84. Meadow SR, Sarsfield. Steroid responsive NS and allergy. Clinical studies. Arch Dis Child 1981;56:509.

85. Mehta KP and Ali U. Recent advances in minimal change nephrotic syndrome. Indian J Pediatr, 1985; 52:579-86.

86. Mehta KP and Ali U, Kutty M. Immunoregulatory treatment for minimal change nephrotic syndrome. Arch Dis Child, 1986; 61 : 153-158.

87. Mehta KP, Chitak AR, Panthaki MH, Nirmal RR, Ali U. Immunoflourescent microscopy in glomerulopathy. Indian Pediatr, 1984; 21 : 701.

88. Michael AF et al. The glomerular mesengium. Kidney Int, 1981; 17 : 141.

89. Moncrieff MW, White RHR, Ogg CS et al. Cyclophosphamide therapy in the nephrotic syndrome in childhood. Br Med J, 1969; 1 : 666.

90. Nash MA, Greifer I, Olbing H et al. The significance of focal sclerotic lesions of glomeruli in children. J Pediatr, 1976; 88 : 806.

91. Norio R. The nephrotic syndrome and heredity. Hum Hend, 1969; 19 : 113.

92. Padmanatham A, Suguna NS, Kunj Ram. Treatment outcome in children with nephrotic syndrome. Indian Pediatr, 1987; 24 : 781.

93. Paul T, Mc Enery MD and Frederic L, Strife MD, Nephrotic syndrome in childhood: Pediatric Clinic North America, 1982; 89(4).

94. Patric Niaudet and French Club of Pediatric nephrology. Steroid resistant idiopathic NS and ciclosporin. Nephron, 1991; 57 : 481.

95. Peter F Hoyer. Letter to editor, cyclosporin in frequency relapsing MCNS. Lancet, 1986; 335.

96. Phadke M, Bhave S, Deptt of Pediatrics, B.J. Medical College, Pune, Indian Pediatr, 1990; 27 : 1035-38.

97. Polito C, Opoao MB, Totino SP, Lammna A and Toro DI. Normal growth of nephrotic syndrome children during long term alternate day prednisolone therapy. Arch Pediatr Scand 1986; 75 : 245-50.

98. Prasad R, Dayal RS, Srivastava VK, Bhatnagar AK, Jain, S and Kapoor S. A clinicopathological study of nephrotic syndrome and role of immunosuppressive therapy. Indian Pediatr, XVII; 1980.

99. Prasad DR, Zimmerman SW, Burkholder PM. Immunohistologic features of MCNS. Arch Pathol Lab Med, 1977; 101 : 348.

101. Rabelink AJ, Navel RJ et al. Editorial Lancet, 1990, 335 : 1045. Partial remission of nephrotic syndrome in patients on long term simvastatin. Editorial Lancet, 1990; 335 : 1045.

102. Rafael Padilla R, Brem AS. Linear growth of children with nephrotic syndrome. Pediatrics 1989; 84 : 495-499.

103. Rance CP, Arbus GS et al. Management of nephrotic syndrome in children. Pediatr Clinc North America, 1976; 23(4).

104. Reader R, Johnson JR and Goulston K. Nephrotic syndrome of acute onset with hypovolemia. Aust, Ann Med, 1962; 11 : 199.

105. Rees L and Chantler G. Growth and endocrine function in children receiving long term steroid therapy for renal disease. Acta Ped Scand Suppl, 1990; 366:93-96.

106. Reeves WJ, Cameron JS. Seasonal nephrotic syndrome, 1975 : 5; 121-37.

107. Rennke HC and Venkatachalam MA. Glomerular permeability : In vivo tracer studies with polyanionic and polycationic ferritins. Kidney Int 1977; 11 : 44.

108. Rolun W, Wahn V, Miller Wiefel DF. Steroid responsive nephrotic syndrome and allergy. Arch Dis Child 1982; 57 : 401-402.

109. Russel J, Merritt, MD, Ph.D., Shirley L Hock, Maryse Kalsch BS, David Olson. Corticosteroid therapy induced obesity in children. Clin Pediatrics, 1986; 15(3) : 150-152.

110. Sarla Vaishnava, Punna Choudhury. Tuberculosis in children with nephrotic syndrome. Indian Pediatr 1983; 20 : 499.

111. Sasdell M, Rovinette C, Cagnoli L et al. Lymphocyte subpopulation in minimal change nephropathy. Nephron, 1980; 25 : 72.

112. Saxena S, Andal A, Saxena HMK. Ultrastructure study of minimal change nephrotic syndrome with clinicomorphological correlation. Indian J Med Res., Aug, 1985; 82 : 171-177.

113. Saxena S, Andal A, Saxena HMK. Idiopathic nephrotic syndrome of childhood - ultrastructural, Immunohistological and clinicopathologic correlation. Indian J Pathol Microbiol 1988; 31(3) : 195-204.

114. Shalhoub BJ. Pathogenesis of lipoid nephrosis. A disorder of T cell function. Lancet, 1974;2:557.

115. Sharples PM, Poultan J and White RHR. Steroid responsive nephrotic syndrome is more common in Asians. Arch Dis Childhood, 1985;60:1014-1017.

116. Siegel NS, Gandio KM, Krassner LS, Mcdonald, BM, Anderson FP, Kashgarian M. Steroid dependent nephrotic syndrome in children: Histopathology and relapses after cyclophosphamide treatment. Kidney Int, 1981; 19 : 454-459.

117. Sobel AT, Intrator L, Lagarne G. Serum immunoglobulins in idiopathic MCNS. N Engl J Med, 1976;294:50.

118. Sonja Kuster, Otto Mehls, Christoffer Seidel, Eberhard Ritz. Blood pressure in minimal change or others types of nephrotic syndrome. Am J Nephrol, 1990; 10(Supple-1) : 76-80.

119. Sohulte Wisser Mann H, Giortz W, Straub E. IgE in patients with glomerulonephritis and MCNS. Eur J Pediatr 1979; 131 : 105.

120. Soyka LF and Saxena KM. Alternate day steroid therapy for nephrotic children. JAMA 1965; 192 : 225.

121. Speck WT, Dresdale SS and Mc Millan RW. Primary peritonitis and the nephrotic syndrome. Am J Surg, 1974; 127 : 267.

122. Srivastava RN, Mayeker G, Anand R et al. Nephrotic syndrome in children. Arch Dis Child 1975; 50:626-30.

123. Srivastava RN, Agarwal RK, Mondgil A and Bhuyan UN. Late resistance to corticosteroids in NS. Jour Pediatrics, 1986; 108 (1) : 66-69.

124. Taube D, Grown Z, Williams DG. Long term impairment of suppressor cell function by cyclophosphamide in MCNS nephropathy and its association with therapeutic response. Lancet, 1981; 1 : 235-238.

125. Thomson PD, Barratt TM, Stokes CR et al. HLA antigens and atopic features in steroid responsive nephrotic syndrome of childhood. Lancet, 1976; 2 : 765.

126. Tiggeler RG, Huline B and Wijueveld PG. Effect of indomethacin on glomerular permeability in the nephrotic syndrome. Kidney Int 1979; 16 : 312.

127. Trainin EB, Boichis H, Spitzer A, Edelmann CM Jr., Griefer I. Late nonresponsiveness to steroid in children with nephrotic syndrome. J Pediatr 1975; 87 : 519.

128. Tyrone Melvin Richard Sibley, Alfred Michael. Nephrotic syndrome in contemporary issues in nephrology. Strauss J (ed), New York, Gailand 1979 : 184.

129. Tyrone Melvin, Richard Sibley, Alfred Michael. Nephrotic syndrome in contemporary kissues in nephrology, Guest editors Bruce M Tune, Stanely Mendoza, Stein JH, Brenner BM, Churchill Living stone, 1984; 190.

130. Ueda N, Kuna K, Ito S. Arch Dis Child, 1990; 65 : 1131-1137.

131. Vazini ND, Paule P, Toohey J, Hong E, Ali Khani S, Darnih R, Pahl MV. Acquired deficiency and urinary excretion of antithrombobin III in nephrotic syndrome. Arch Intern Med 1984; 144 : 1802.

132. Vaziri ND. Nephrotic syndrome and coagulation and fibrinolytic abnormalities. Am J Nephrol, 1983; 3:1.

133. Veehaskari VM et al. Glomerular charge and urinary protein excretion. Effects of systemic and intra-renal polycation infusion in the rat. Kidney Int, 1982; 22 : 127.

134. Vega GL et al Lovastatin therapy in nephrotic hyperlipidemic effects on lipoprotein metabolism. Kidney Int 1988; 33 : 1160-8.

135. Venkatachalam MA and Rennke HG. Structural and molecular basis of glomerular filtration. Circ Res, 1978; 43 : 337.

136. Verneir RL. Primary (Idiopathic) nephrotic syndrome In : Pediatric nephrology eds. Holiday MA, Barrat TM, Vernier RL, Baltimore, Williams and Willkins, 1987; 445-446;

137. Wagoner RD et al. Renal vein thrombosis in idiopathic membranous glomerulopathy and nephrotic syndrome. Incidence and significance. Kidney Int 1983; 23 : 368.

138. Waldnerr R, Gubles MC, Levy M. The significance of pure diffuse mesengial proliferation in idiopathic nephrotic syndrome. Kidney Int 1983; 23 : 368-74.

139. Wilfert CM and Katz SL. Etiology of bacterial sepsis in nephrotic children. Pediatrics 1968; 42 : 840.

140. William F, Keane MD, Bertran L, Kasiske MD. Hyper lipidemia in NS. New Eng J Med 1990; 323; 409 : 603-04.

141. Williams SA, Makker SP, Ingelfinger JR et al. Long term evaluation of chlorambucil plus prednisolone in the idiopathic nephrotic syndrome of childhood. N Engl J Med 1980; 302 : 929.

142. White RHR. The nephrotic syndrome. In Gairdner D, and Hull D (eds.). Recent advances in Pediatrics. Edition 4, London, J & A Churchill, 1971 : 281.

143. White RHR, Glasgow EF and Mills RJ. Clinicopathological study of nephrotic syndrome of childhood. Lancet, 1970; J, 1353.

144. White RHR. The familial nephrotic syndrome. Int Arch Eur Surg Clin Nephrol 1973; 1 : 215-29.

145. Yaceoglu AM, Berkuyich S and Chin J. Effect of live measles virus vaccine on childhood nephrosis. J Pediatr 1969; 74 : 291.

146. Yokoyama H, Kida H, Tani Y, Abe T, Tomosugi N, Koshino Y and Hattori N. Immunodynamics of minimal change nephrotic syndrome in adults T and B lymphocyte subsets and serum immunoglobulin levels. Clin Exp Immunol 1985; 61 : 601-607.

147. Zelleruelo G, Hsia SL, Freindlich M, Gorman HM, Strauss J. Persistence of lipid abnormalities in children with idiopathic nephrotic syndrome. J Pediatric, 1984; 104 : 61-64.
